PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61M 5/00 — A1

(11) International Publication Number: WO 91/03267

(43) International Publication Date: 21 March 1991 (21.03.91)

(21) International Application Number: PCT/US89/04035

(22) International Filing Date: 15 September 1989 (15.09.89)

(30) Priority data:
399,943 — 28 August 1989 (28.08.89) — US

(71)(72) Applicants and Inventors: SEKINS, K., Michael [US/US]; 17218 S.E. 40th Place, Bellevue, WA 98008 (US). SHAFFER, Thomas, S. [US/US]; 159 Bryn Mawr Avenue, Lansdowne, PA 19050 (US). WOLFSON, Maria, R. [US/US]; 806 East Graves Lane, Wyndmoor, PA 19118 (US).

(74) Agent: MASON, John, B.; Christensen, O'Connor, Johnson & Kindness, 2800 Pacific First Centre, 1420 Fifth Avenue, Seattle, WA 98101 (US).

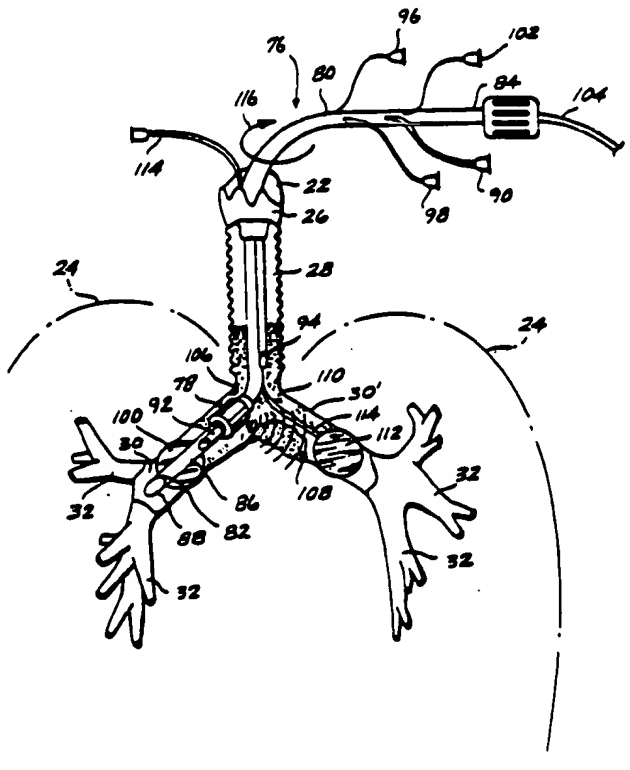
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent)*, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
With amended claims.

(54) Title: LUNG CANCER HYPERTHERMIA VIA ULTRASOUND AND/OR CONVECTION WITH PERFLUOROCARBON LIQUIDS

(57) Abstract

A hyperthermic treatment of lung cancer, by temporarily filling with a liquid medium (110) preselected pulmonary air passages (30') adjoining pulmonary tissues containing malignant cells (108), circulating exogenously or intracorporally, ultrasonically heated liquid medium (110) at from about 41 °C to about 50 °C through the liquid-filled pulmonary air passages (30, 30'), and thereafter removing the liquid medium (110). The liquid medium (110) may be a perfluorocarbon liquid or physiological saline solution. Suitable perfluorocarbon liquids are characterized by an average molecular weight in the range of from about 350 to about 560 for exogenously heated liquids, e.g. FC-84, FC-72, RM-82, FC-75, RM-101 and perfluorodecalin; or in the range of from about 400 to about 500 for intracorporally, ultrasonically heated liquids. Also, liquid infusion and isolation catheters (20), intracavitary ultrasound applicators (76, 130), and intercostal ultrasound applicators (66, 68) for the disclosed convection and/or ultrasound hyperthermia treatments of lung cancer.



LUNG CANCER HYPERTHERMIA VIA ULTRASOUND AND/OR CONVECTION WITH PERFLUOROCARBON LIQUIDS

This invention was made with government support under Small Business Innovation Research Program Grant No. 1 R43 CA48611-01 awarded by the Public Health Service, Department of Health and Human Services. The government has certain rights in the invention.

Technical Field

The invention relates to methods and means for introducing liquids into the lungs of cancer patients to effect hyperthermic treatment and augmented radiotherapy and chemotherapy of lung cancer.

Background of the Invention

In the United States there has been a steady rise in the age-adjusted national death rate from cancer (all types) since the early part of the century. The overwhelmingly predominant contributor to this trend is lung cancer. Currently about 8% of all deaths in the industrialized world are attributed to lung cancer. In the United States, an estimated 155,000 new cases of lung cancer are currently diagnosed each year, and about 142,000 will die of the disease, about 1 death every 4 minutes! Only about 10% of the patients currently diagnosed with lung cancer will survive beyond 5 years.

Lung cancer, or bronchial carcinoma, refers strictly to tumors arising from the major airways (bronchi) and pulmonary parenchyma (bronchioles, alveoli, and supporting tissue), as opposed to those metastasizing from other sites. The four major forms of lung cancer, squamous cell carcinoma (SCC), adenocarcinoma (AC), large cell anaplastic carcinoma (LCAC), and small cell anaplastic carcinoma (SCAC), account for 98% of pulmonary malignancies. Although lung cancer can occur anywhere in the lungs, about three-quarters of primary lung cancers occur in and/or on the bronchial walls within the first three bronchial generations, i.e., near or proximal to the hilus, the region where the airways and major vessels

enter and leave each lung. A smaller percentage occur in more distal areas of the parenchyma. Many tumors occur near the carina, at the junction of the right and left bronchi with the trachea, presumedly due to increased deposition of inhaled carcinogens. Squamous cell carcinoma tumors, the most common histological type, making up 30-40% of lung tumors, arise inside the surface layer of the bronchial wall and then invade the wall and adjacent structures. Squamous cell carcinomas tend to be relatively localized with less tendency than the other lung cancer tumors to metastasize. Adenocarcinoma tumors, also comprising 30-40% of lung cancers, occur in the mid- to outer third of the lung in about three-quarters of the cases. Adenocarcinomas tend to metastasize widely and frequently to other lung sites, the liver, bone, kidney, and brain. Small cell cancer, accounting for about 20% of all lung cancer, is the most aggressively metastatic and rapidly growing, and can begin near the hilus or in the lung periphery. Large cell tumors account for only a few percent of lung cancer and can occur anywhere in the lung. "Local failure," where primary tumors spread to mediastinal lymph nodes, pleura, adrenal glands, bone, and brain, is common with adenocarcinoma, small cell anaplastic carcinoma, and large cell anaplastic carcinoma, and less so in squamous cell carcinoma.

The current "curative" treatment for lung cancer is surgery, but the option for such a cure is given to very few. Only about 20% of lung cancer is resectable, and out of this number less than half will survive five years. Radiation therapy (RT) is the standard treatment for inoperable non-small cell cancer, and chemotherapy (alone or with radiation therapy) is the treatment of choice for small cell and other lung cancer with wide metastasis. Patients with clinically localized but technically unresectable tumors represent a major problem for the radiotherapist, accounting for an estimated 40% of all lung cancer cases.

Adjunctive hyperthermia, the use of deep heating modalities to treat tumors, is being used increasingly to augment the therapeutic efficacy of radiotherapy and chemotherapy in cancer treatment. It has been estimated that eventually "hyperthermia will be indispensable for 20 to 25% of all cancer patients" [1; see the appended listing of literature citations]. Hyperthermia clinical research is increasingly showing the importance of using specialized heating equipment to treat specific anatomical locations and sites rather than devices with more general-purpose heating capabilities. Unfortunately, current hyperthermia devices are ill-suited to providing deep, localized heating of lung cancer. Because of this limitation, very few applications of localized lung hyperthermia have been recorded in the literature [2].

Kapp [8] has shown that, in terms of absolute numbers of patients (15,000 in 1987), more lung cancer patients would benefit from effective local hyperthermia than in any other cancer category, with the possible exception of prostate carcinoma. Because of the present difficulty of heating tumors locally in a controlled fashion in the center of the thorax, the techniques most commonly attempted for lung cancer hyperthermia to date have been whole-body hyperthermia (WBH), and radio-frequency (RF) heating of locoregional lung areas [2,9]. While whole-body hyperthermia has produced some encouraging results in combination with chemotherapy, the technique is unsatisfactory since it produces significant systemic toxicity and mortality, and because the thermal dose is limited due to long induction times (warmup) and the need to maintain core temperatures below 42°C. The electromagnetic (EM) approaches to lung heating have also been disappointing, due to the unpredictability of the heating patterns produced, the difficulty of measuring intratumoral temperatures in electromagnetic fields, the propensity of radio-frequency heating to preferentially heat superficial fat, and because of the physical inability of electromagnetic modalities to produce small focal volumes. The modern microwave body-surrounding array systems also suffer from difficulties associated with localization and predictability of heating, thermometry artifacts, and heat spikes at fat muscle interfaces.

Because of its characteristically small wavelengths, therapeutic ultrasound has the best capability for providing local heating in the body of all the conventionally used hyperthermia modalities. Focused and unfocused ultrasound beams are routinely used clinically to successfully provide localized hyperthermia to many tumors residing in soft tissues and organs. However, the presence of air in the lung has precluded this valuable energy source from being applied to lung hyperthermia.

Thus, the need for a means of delivering safe, effective, and well-tolerated localized heating to lung tumors is clear. The invention solves this problem, in the preferred embodiment, by an unconventional use of perfluorocarbon liquids and therapeutic ultrasound.

Perfluorocarbon (PFC) liquids are derived from common organic compounds by the replacement of all carbon-bound hydrogen atoms with fluorine atoms. They are clear, colorless, odorless, nonflammable, and essentially insoluble in water. They have extremely high dielectric strength and resistivity. They are denser than water and soft tissue, have low surface tension and, for the most part, low viscosity. Perfluorocarbon liquids appear to have the lowest sound speeds of all liquids and are also unique in their high affinity for gases, dissolving up to 20

times as much O_2 and over three times as much CO_2 as water. Like other highly inert carbon-fluorine materials which are widely used in medicine (e.g., in drugs, Teflon™ implants, blood oxygenator membranes, etc.), perfluorocarbon liquids are extremely nontoxic and biocompatible. For a review, see: Biro, P.B., and P. Blais, Perfluorocarbon blood substitutes, in CRC Critical Reviews in Oncology/Hematology, Vol. 6, No. 4, pp. 311-374, 1987, which is hereby incorporated by reference.

To date, about 300 liquid compounds have been investigated for blood-gas exchange applications [4]. Those liquids which have evolved as artificial blood substitutes are complex perfluorocarbon liquid-based aqueous emulsions containing various chemical stabilizers and viscosity modifiers, along with conventional parenteral additives (glucose, electrolytes, starch, and buffers). Compatibility with blood and a surprising lack of major adverse effects have been demonstrated in several animal species. The first administration of perfluorocarbon liquid blood substitute (Fluosol-DA, one of four commercial blood substitutes now available) to human volunteers occurred in 1978 [10], with the first clinical use taking place shortly after in 1979 [11,12]. Subsequently, numerous other studies have been carried out in Japan, the United States, Canada, and Europe that have confirmed the comparatively benign impact of infusing significant amounts (some tests used liters) of the perfluorocarbon/water emulsions directly into the systemic blood circulation [13,14,15]. The blood substitutes are not yet ready for general clinical systemic use for two reasons: a) the requirement to form an emulsion to suspend the perfluorocarbon particles significantly reduces the volume fraction of the gas carrier (the perfluorocarbon), thus large volumes must be infused, and b) the emulsion gradually coalesces as it circulates, leading to premature removal of many of the synthetic constituents from the blood. However, studies are currently ongoing in a number of clinically related therapeutic perfluorocarbon applications primarily taking advantage of the oxygen carrying capacity of blood substitute emulsions [16,17,18,19].

It was first demonstrated that mammals submerged in hyperoxygenated saline could breathe liquid and successfully resume gas breathing in 1962 [20]. However, this approach to liquid ventilation (LV) was eventually abandoned, due to the practical difficulties of dissolving sufficient quantities of O_2 in saline (done under high pressure), and because saline rinses away much of the surfactant lining the lung alveoli [21]. These problems were overcome in 1966, by Dr. Leland Clark [22], who was the first to use perfluorocarbon liquids (now oxygenated at atmospheric pressure) to support the respiration of mice, cats, and puppies. The

extreme biocompatibility and suitable properties of certain perfluorocarbon liquids has subsequently led to a significant body of ongoing research yielding promising clinical applications.

To date it has been clearly established that mammals can breathe (total ventilation support) oxygenated perfluorocarbon liquids for long periods (> 3 hours) and return to gas breathing without untoward long-term effects [23, 24]. In addition, studies have also shown that no adverse morphological, biochemical, or histological effects are seen after perfluorocarbon ventilation [24, 25, 26]. Perfluorocarbon liquids have also been investigated for lung lavage (washing) [27], and have been found to be effective for rinsing out congestive materials associated with Respiratory Distress syndrome (RDS) in adult humans [28]. While total respiratory support of both lungs via perfluorocarbon liquids is not without side effects, they are minor and transient (mild acidosis, lower blood pO_2, and increased pulmonary vascular resistance and decreased lung compliance) [3, 29, 30, 31]. Other biomedical applications of perfluorocarbon liquid ventilation have also received serious research effort [32, 33].

Pertinent to convective lung hyperthermia, i.e., lung heating by the repetitious infusion and removal of hot liquids to and from the lung, studies of the physiological heat exchange occurring from high- and low-temperature perfluorocarbon ventilation of animals have also been performed [30,41,42]. These studies have involved complete-lung liquid heating and cooling, and have been done at only moderate temperatures, but have illuminated and quantified many relevant physiological responses and systemic temperature effects. A very recent study [43] reporting hyperthermic (to 45°C) convection heating of lungs involved sustained heating of surgically isolated dog lung lobes via heated blood perfusion, i.e., heating induced from the blood side rather than the airway side. Taking measurements of lung edema, compliance, perfusion pressure, and serotonin uptake during 2-hour sustained hyperthermia (done at 37.6°, 40.7°, and 44.5°C, time-averaged lung temperatures), no significant changes in lung parameters were found other than expected increases in perfusion pressure with temperature. The authors conclude that a normal lung appears to tolerate well the sustained heating regimens appropriate for cancer hyperthermia applications.

However, the problem of how to effect controlled and sufficiently localized hyperthermia of malignant lung tissue has until now remained unsolved.

Summary of the Invention

The invention provides, in one embodiment, a hyperthermic treatment of lung cancer, which includes the steps of: temporarily filling with a liquid medium

preselected pulmonary air passages adjoining pulmonary tissues containing malignant cells, circulating exogenously heated liquid medium having a temperature in the range of from about 41° to about 50°C (preferably from about 42° to about 45°C) through the liquid-filled pulmonary air passages for a predetermined period of time, and thereafter removing the liquid medium from the pulmonary air passages of the patient. The liquid medium may be a perfluorocarbon liquid or physiological saline solution. Suitable perfluorocarbon liquids having the requisite physical and thermal properties are characterized by an average molecular weight in the range of from about 350 to about 560 and by having: a viscosity less than about 5 CP at 25°C, a density less than about 2.0 g/cm^3 at 25°C, a boiling point greater than about 55°C, a vapor pressure in the range of from about 20 Torr to about 200 Torr, and a Prandtl number less than about 10 at 25°C. Representatives of such perfluorocarbon liquids are FC-84, FC-72, RM-82, FC-75, RM-101, and perfluorodecalin. The preferred group of perfluorocarbon liquids is characterized by having an average molecular weight in the range of from about 420 to about 460, a vapor pressure less than about 100 Torr at 25°C, and a surface tension less than about 17 dynes/cm at 25°C.

The invention also provides a hyperthermic treatment of lung cancer using ultrasound, including the steps of: temporarily filling with a liquid medium preselected pulmonary air passages adjoining pulmonary tissues comprising malignant cells, heating the adjoining pulmonary tissues comprising the malignant cells to a temperature in the range of from about 41° to about 50°C (preferably from about 42° to about 45°C) for a predetermined period of time by transmitting ultrasound through the liquid-filled pulmonary air passages, and thereafter removing the liquid medium from the pulmonary air passages of the patient. Perfluorocarbon liquids having the requisite physical, thermal, and acoustic properties for this ultrasound treatment are characterized by an average molecular weight in the range of from about 400 to about 560. Such perfluorocarbon liquids are also characterized by having: viscosity less than about 5 CP at 25°C, density less than about 2.0 g/cm^3 at 25°C, boiling point greater than about 75°C, vapor pressure in the range of from about 25 Torr to about 100 Torr, surface tension below about 17 dynes/cm at 25°C, acoustic impedance in the range of from about 0.8 to about 1.6 MegaRayls at 37°C, and acoustic attenuation less than about 1.2 dB/cm (at 1.0 MHz, 45°C, and acoustic intensity of about 3 W/cm^2). The preferred group of perfluorocarbon liquids for this purpose is characterized by an average molecular weight in the range of from about 420 to about 460, and representative of these are FC-75, RM-101, and perfluorodecalin.

Operable and preferred ultrasound frequency ranges are also disclosed, for use with different liquid-filled regions of the pulmonary air passages. The ultrasound may be produced by a transducer disposed within the liquid-filled pulmonary air passages, or the transducer may be disposed exogenous to the liquid-filled pulmonary air passages. For example, the ultrasound may be transmitted through an intercostal space of the patient, or it may be transmitted from an exposed surface of the lung into the volume of same during an intra-operative application involving an "acoustic window" into the lung created by surgical means.

Also provided are liquid infusion and isolation catheters, intracavitary ultrasound applicators, and intercostal ultrasound applicators for practicing the disclosed convection and/or ultrasound hyperthermia treatments of lung cancer.

Brief Description of the Drawings

FIGURE 1 depicts a representative liquid infusion and isolation catheter according to the invention;

FIGURE 2 depicts a pair of representative intercostal ultrasound applicators;

FIGURE 3 shows a representative intracavitary ultrasound applicator, and also an optional cuff plug;

FIGURE 4 shows the construction of a representative intracavitary transducer assembly;

FIGURE 5 shows another representative intracavitary ultrasound applicator;

FIGURE 6 illustrates in greater detail the representative transducer assembly shown in FIGURE 5;

FIGURE 7 is a graph indicating the molecular weights (y-axis) of representative perfluorocarbon liquids (x-axis);

FIGURE 8 is a graph indicating the surface tension (dynes/cm) of representative perfluorocarbon liquids;

FIGURE 9 is a graph indicating the viscosity at 25°C (CP) of representative perfluorocarbon liquids;

FIGURE 10 is a graph indicating the density at 25°C (g/cm^3) of representative perfluorocarbon liquids;

FIGURE 11 is a graph indicating the oxygen solubility (ml/100ml) of representative perfluorocarbon liquids;

FIGURE 12 is a graph indicating the boiling point (°C) of representative perfluorocarbon liquids;

FIGURE 13 is a graph indicating the vapor pressure (Torr) of representative perfluorocarbon liquids;

FIGURE 14 is a schematic depiction of a representative acoustical test system, wherein the following abbreviations apply: VP, vacuum pump; VV, vacuum vent; VG, vacuum gauge; OS, O_2 sensor; P/VG, pressure/vacuum gauge; FI, fluid inlet; DVV, degassing vacuum vessel; CRH, cal rod heater; EG, equilibrium gases; V, variac; RP, recirculation pump; T, thermocouple; PT, U.S. power transducer; FSC, fluid sample cell (650 ml); BP, base plate; and ASP, acoustic absorber plate;

FIGURE 15 is a graph indicating the velocity of sound (km/sec) in representative perfluorocarbon liquids;

FIGURE 16 is a graph indicating the acoustic impedance (MegaRayls) and speed of sound (m/sec) of selected tissues (panel A, wherein: *a* indicates muscle; *b*, blood; *c*, water; and *d*, fat) and representative perfluorocarbon liquids (panel B) at 37°C, wherein the empty bars represent impedance and the solid bars represent sound speed;

FIGURE 17 is a graph indicating the acoustic impedance (Rayls x 10^6) of representative perfluorocarbon liquids as compared with water;

FIGURE 18 is a graph indicating the relationship between perfluorocarbon (FC-43) cavitation threshold (W/cm^2) and temperature (°C) as a function of gas saturation (7% O_2, 7% CO_2, balance N_2) at 900 KHz, wherein: *a* indicates 95.8% saturation; *b*, 98.3% sat.; *c*, 100% sat.; and *d*, the maximum power used;

FIGURE 19 is a graph depicting acoustic losses in perfluorocarbon liquids by plotting the relationship between perfluorocarbon acoustic intensity (y-axis) and electrical intensity (x-axis) at 1.0 MHz and 25°C, wherein loss through a liquid FC-75 path (solid circles) is compared with a loss-free water path (open squares);

FIGURE 20 is a graph depicting acoustic losses in perfluorocarbon liquids by plotting the relationship between perfluorocarbon acoustic intensity (y-axis) and electrical intensity (x-axis) at 0.5 MHz and 25°C, comparing FC-75 (solid circles) and water (open squares) paths;

FIGURE 21 is a graph depicting acoustic losses in perfluorocarbon liquids by plotting the relationship between perfluorocarbon acoustic intensity (y-axis) and electrical intensity (x-axis) at 0.25 MHz and 25°C, comparing FC-75 (solid circles) and water (open squares) paths;

FIGURE 22 is a graph indicating the relationship between perfluorocarbon (FC-75) attenuation (y-axis) and acoustic intensity (x-axis) as functions of temperature (25° or 45°C, represented respectively by open and solid symbols) and frequency (MHz);

FIGURE 23 is a graph indicating the relationship between acoustic intensity (y-axis) and electrical intensity (x-axis) for FC-75 at 0.25 MHz and 45°C, comparing FC-75 (solid circles) and water (open squares) paths;

FIGURE 24 is a graph of acoustic intensity (y-axis) versus electrical intensity (x-axis), indicating the attenuation range of various perfluorocarbons at 1.0 MHz and 25°C, wherein FC-84 (open squares), FC-75 (solid circles), and FC-43 (solid triangles) are compared;

FIGURE 25 is a graph of acoustic intensity (y-axis) versus electrical intensity (x-axis), indicating the attenuating effects of gas saturation in perfluorocarbon FC-75 at 1.0 MHz and 25° or 45°C, wherein the square symbols represent degassed liquids, the circular symbols represent saturated liquids, and *a* represents conditions in which cavitation was detectable;

FIGURE 26 is a graph of attenuation coefficient (y-axis) versus frequency (x-axis), showing *in vivo* perfluorocarbon (FC-75)-filled lung attenuation in the right apical lobe at various frequencies (MHz), wherein 1.0 MHz is represented by the solid circle and the open diamonds ($\Delta T/\Delta t$ and hydrophone, respectively) and 2.25 MHz (hydrophone) by the open triangles;

FIGURE 27 is a graph of sound speed (y-axis) versus temperature (x-axis), indicating the predominance of perfluorocarbon FC-75 (dashed line) in establishing the sound speed in liquid-filled lungs, wherein *in vitro* PFC-filled lung at 1.0 MHz is indicated by the solid triangle, *in vitro* PFC-filled lung at 2.25 MHz by the open square, and *in vivo* PFC-filled lung at 1.0 MHz by the solid square, as compared with blood (solid circles) and muscle (open diamonds);

FIGURE 28 is a graph of lung temperature (y-axis) versus treatment time (x-axis), demonstrating ultrasound hyperthermia of perfluorocarbon-filled pulmonary air passages in the cranial segment of the right apical lobe, wherein *a* indicates 0.5 cm, *b* indicates 1.0 cm, *c* indicates 2.0 cm, *d* indicates 3.0 cm, *e* indicates dist. surf. (w/abs.), and *f* indicates thoracic cavity;

FIGURE 29 is a schematic diagram of the Large Animal Liquid Ventilation System at Temple University, wherein the following abbreviations apply: A, animal; HE, heat exchanger; MO, membrane oxygenator; OS, O_2 source; EP, expiratory piston; SA, system actuator; IP, inspiratory piston; CTBC, constant temperature bath and circulator; and LR, liquid reservoir;

FIGURE 30 is a graph of tissue temperature (y-axis) versus treatment time (x-axis), demonstrating perfluorocarbon FC-75 convection lung hyperthermia as a function of tidal volume (V_t) and liquid inspiration temperature (T_{ins}), wherein *a* indicates lung interstitium, *b* indicates inter-lobar, *c* indicates deep muscle, and *d* indicates setup;

FIGURE 31 is a graphical depiction of normalized intensity (y-axis) versus ultrasound beam profiles at 1.0 MHz (x-axis) from two representative intracavitary applicators *a* and *b*;

FIGURE 32 is a graphical depiction, in terms of normalized SAR (y-axis) at 2 cm depth versus axial position (x-axis), of intracavitary phantom SAR profiles at 1.0 MHz from two representative intracavitary applicators *c* and *d*;

FIGURE 33 is a graphical depiction of intracavitary applicator axial SAR profiles, in terms of normalized SAR (y-axis) at 1.0 MHz versus axial position (x-axis), for two representative intracavitary applicators, showing the midline (240° seg) SAR at the three indicated depths (0.0, 1.0, and 2.0 cm); and,

FIGURE 34 is a schematic diagram of a representative liquid-filled lung convection hyperthermia and liquid infusion system, wherein the following abbreviations apply: IP, insp. pump; EP, exp. pump; ITP, insp. temp. probe; ETP, exp. temp. probe; IFM, insp. flow meter; EFM, exp. flow meter; IR, insp. reservoir; ER, exp. reservoir; CV, check valve; IRTP, insp. res. temp. probe; GCP, gas circular pump; FS, free surface; CHE, cooling heat exchanger; H, heater; G/DV, gas/degas vessel; C, condenser; VP, vacuum pump; and C/MC, central/ monitoring computer.

Detailed Description of the Preferred Embodiments

The invention provides, in one embodiment, a method of treating lung cancer by convection hyperthermia. Preselected pulmonary air passages that adjoin pulmonary tissues containing malignant cells are temporarily filled with a liquid medium such as physiological saline solution or, preferably, a perfluorocarbon liquid. By "pulmonary air passages" is meant the pulmonary channels, spaces or volumes in the trachea, left and right bronchi, bronchioles, and alveoli of the lungs that are normally occupied by air. In the practice of the invention, only the pulmonary air passages in contact with or near a patient's tumor site(s) are typically filled with the liquid medium, and gaseous ventilation of the remaining pulmonary air passages is maintained. Depending on the location of the lung cancer, as determined by available diagnostic methods, the fluid-filled pulmonary air passages may be localized in a lung, lobe or lung segment, and/or the bronchial tree may be selected for localized filling with the liquid medium. Localized filling of the pulmonary air passages in such a preselected manner can be effected by means of the representative infusion catheters described below. Diagnostic ultrasonic imaging can be used to monitor the filling of the pulmonary air passages, if either physiological saline or a perfluorocarbon liquid serves as the

liquid medium. During the filling step, the perfluorocarbon liquid is preferably degassed at least 50%, and is most preferably substantially (almost totally) degassed.

To effect the localized convection hyperthermia treatment, exogenously heated liquid medium having a temperature in the range of from about 41° to about 50°C, and preferably from about 42° to about 45°C, is circulated through the liquid-filled pulmonary air passages for a period of time that may be determined at the discretion of the attending physician. During, prior to or subsequent to this hyperthermic treatment, the malignant cells may be irradiated with ionizing radiation such as x-rays, electron beams, neutron beams, etc. To potentiate the effects of such radiation treatments, the liquid medium in the fluid-filled pulmonary air spaces may be oxygenated. In treatments where the preselected pulmonary air passages are initially filled with substantially degassed perfluorocarbon liquid, exogenously heated oxygenated perfluorocarbon liquid may be circulated into the liquid-filled pulmonary air passages after the filling process is complete, prior to and/or during irradiation of the malignant cells with the ionizing radiation.

The circulating liquid medium may also contain a therapeutic agent such as an anti-cancer drug (e.g., adriamycin), toxin, antibody-linked radionuclide, etc. In treatments where the adjunctive use of such water-soluble therapeutic agents is desirable, the liquid medium may be an aqueous perfluorocarbon liquid emulsion.

After the hyperthermic treatment period, which as mentioned will vary in a patient-specific manner, depending partly upon the tumor location and any adjunctive therapies employed, the liquid medium is removed from the pulmonary air passages of the patient.

A preferred liquid medium for this convection hyperthermia treatment is a perfluorocarbon liquid of the general type used for lung ventilation. Suitable perfluorocarbon liquids having the requisite thermal as well as physical properties for use in convection pulmonary hyperthermia include perfluorocarbon liquids characterized by an average molecular weight, of the perfluorocarbon constituent(s), in the range of from about 350 to about 560. Such perfluorocarbon liquids are alternatively characterized by having a viscosity less than about 5 CP at 25°C, a density less than about 2.0 g/cm^3 at 25°C, a boiling point greater than about 55°C, a vapor pressure greater than about 20 Torr but less than about 200 Torr at 25°C, a surface tension less than about 17 dyne/cm at 25°C, and a Prandtl number less than about 10 at 25°C. To provide some adjunctive respiratory support, and for use with radiation therapy, and to provide efficient lung

filling in the degassed state, the perfluorocarbon liquid should also have an oxygen solubility greater than about 40ml/100ml. Representative perfluorocarbon liquids that meet the above criteria include FC-84, FC-72, RM-82, FC-75 (3M Company, Minneapolis, MN), RM-101 (MDI Corporation, Bridgeport, CN), dimethyladamantane (Sun Tech, Inc.), trimethylbicyclononane (Sun Tech, Inc.), and perfluorodecalin (Green Cross Corp., Japan). The preferred group of perfluorocarbon liquids, in terms of optimizing the operative combination of physical and thermal properties, are characterized by an average molecular weight in the range of from about 400 to about 460. Such perfluorocarbon liquids are characterized by having a vapor pressure less than about 100 Torr. The most preferred perfluorocarbon liquids have an average molecular weight in the range from about 420 to about 460, and representative of this group are FC-75, RM-101, and perfluorodecalin.

The invention also provides an ultrasonic hyperthermic treatment of lung cancer. In this embodiment, after the preselected pulmonary air passages adjoining the patient's malignant cells are filled with the liquid medium such that an adequate and appropriate acoustic transmission path has been established, the pulmonary tissues containing the malignant cells are heated to a temperature in the range of from about 41° to about 50°C by transmitting ultrasound through the liquid-filled pulmonary air passages. In a preferred embodiment, the ultrasound is produced by an intracavitary transducer that is positioned within the liquid-filled pulmonary air passages. Alternatively, the transducer may be located exogenous to the pulmonary air passages. For example, the ultrasound can be transmitted through an intercostal space between the ribs of the patient, or the transducer can be applied to the pulmonary pleura or lung surface overlying the fluid-filled passages, following surgical displacement of ribs or other interfering tissues.

In order to serve as a suitable acoustical propagating medium in this ultrasonic hyperthermic treatment, the perfluorocarbon liquid should have the following physical, thermal, and acoustical properties: viscosity less than about 5 CP at 25°C, density less than about 2.0 g/cm^3 at 25°C, boiling point greater than about 75°C, vapor pressure greater than about 25 Torr and less than about 100 Torr, acoustic impedance between about 0.8 to about 1.6 MegaRayls at 37°C, and acoustic attenuation less than about 1.2 dB/cm (±20%) at 1.0 MHz, 45°C, and acoustic intensity of about 3 W/cm^2. The perfluorocarbon liquid is preferably also characterized by an oxygen solubility greater than about 40ml/100ml. Perfluorocarbon liquids having an average molecular weight in the range of from about 400 to about 500 generally satisfy the above criteria, with the preferred group in

terms of optimizing the thermal and acoustical properties having an average molecular weight in the range of from about 400 to about 460, and most preferably in the range of about 420 to about 460. Representative of this most preferred group of perfluorocarbon liquids are FC-75, RM-101, and perfluorodecalin.

In treatments where the preselected liquid-filled pulmonary air spaces are localized in the bronchial tree, the ultrasound from an intracavitary transducer preferably has a frequency in the range of from about 250 KHz to about 3 MHz, and most preferably from about 500 KHz to about 2 MHz. For peripheral lung treatments (i.e., in the membranous airways and alveoli of the lung), where the sound waves must necessarily traverse many more liquid-tissue interfaces, a lower ultrasound frequency in the range of from about 250 KHz to about 1.5 MHz is necessary when perfluorocarbon liquids serve as the liquid medium. Ultrasound frequencies in the latter range are also recommended when the transducer is positioned exogenous to the lung.

The desired frequency within these ranges is established on the basis of the depth of heating sought. Lower frequencies are attenuated less and, therefore, are employed where deeper heating is preferred. Conversely, higher frequencies are more readily absorbed, and thus are more appropriate for more superficial heating. Optimal treatments may include a combination of the following strategies. First, a single transducer may broadcast at more than one frequency to effect a desired heating pattern. The changes in frequency in this case may be done by rapid incremental changes in frequency over a specified bandwidth using frequency modulation (FM) methods, or they may be done with serial changes over time whereby sound (in FM mode or not) is generated in predetermined frequency ranges for desired periods and then changed to other frequencies for periods of time. Second, multiple transducers (focused, diverging, or unfocused) may be employed to operate in tandem at similar or different frequencies (in FM mode or not) to effect desired heating patterns.

Where physiological saline serves as the liquid propagating medium, the ultrasound can be in the frequency range of from about 250 KHz to about 3 MHz from intracavitary transducers, and in the range of from about 500 KHz (preferably about 750 KHz) to about 3 MHz from exogenous transducers.

While the perfluorocarbon liquid is preferably degassed during the filling step, oxygenation of the liquid may be desirable (e.g., for radiation treatment or respiratory support) during the ultrasonic hyperthermic treatment. However, in order to suppress cavitation, the dissolved gas content (including oxygen, air,

nitrogen, carbon dioxide or other gases) of the perfluorocarbon liquid in the liquid-filled pulmonary air passages should be held at no more than about 75% of saturation for ultrasonic treatments in the 2-3 MHz range. No more than about 50% of saturation should be permitted for ultrasonic treatments in the 250 KHz to 1.5 MHz range. The requisite dissolved gas content can be maintained by circulating the perfluorocarbon liquid into and out of the lung during the treatment between the liquid-filled pulmonary air passages and an extraneous source of gas-content processing, such as a degassing chamber.

The invention also provides liquid infusion catheters, intracavitary ultrasound applicators, and exogenous ultrasound transducers, representative embodiments of which are shown in FIGURES 1-5. Prior bifurcated bronchial catheters that have been used for delivering liquid into a lung are not suitable for use in the subject convection and ultrasonic hyperthermia treatments, for a number of reasons. First, the subject treatments can be applied deeper in the lung than heretofore possible, and prior commercial devices lack sufficient flexibility and length to reach many of the segmented bronchi. In addition, the inflatable cuff material used in the prior devices tends to lose its structural integrity at the relatively high fluid temperatures involved in the subject treatments. Furthermore, the prior devices are in general too large in diameter to penetrate several of the pertinent segmental bronchial passageways in the lungs, and they also provide no instrumentation for monitoring local transient and steady state temperature, and pressure, and are ill-suited for positional information.

Referring initially to FIGURE 1, a representative embodiment of the subject liquid infusion and isolation catheter 20 is shown in conjunction with the pulmonary air passages 22 that lead to and ramify throughout the lungs 24. More particularly, catheter 20 is shown passing through the larynx 26 and trachea 28 and into a bronchus 30 and associated segmental bronchi 32.

Catheter 20 includes a flexible conduit 34 having a distal end 36 that is positioned, in this instance, within segmented bronchus 32, and a proximal end 38 that is positioned outside (or exogenous to) the patient. The representative embodiment shown in FIGURE 1 has a pair of inflatable cuffs 40 and 42 formed near the distal end 36 that are in fluid (liquid or gaseous) communication with corresponding channels 44 and 46 that exit the conduit 34 near the proximal end 38. Also shown at the proximal end 38, a liquid inlet/outlet connector 48 is in fluid communication through a liquid passageway 51 with an opening 50 at the distal end 36 of conduit 34. A gas ventilation channel 52 also is formed in the conduit 34 to be in fluid communication with a ventilation port 53 positioned so as

to ventilate the bronchial tree. A pressure sensor 54 and temperature sensor 56 are positioned near the distal end 36, and have lead wires 58 and 60, respectively, passing through the conduit 34 and exiting at the proximal end 38. The temperature sensor 56 may take the form of a thermistor, thermocouple, resistance-based temperature device, etc. Suitable pressure sensors 54 include: solid-state piezoresistive diaphragm-based sensors, semiconductor strain gage sensors, etc.

The conduit 34 is typically formed from flexible plastics, such as a Teflon™, silicon rubber, polyurethanes, polyvinylchloride, Delrin™, or acetyl copolymers, or combinations thereof, having an outer thermal insulation layer 64 formed, for example, of a closed-cell plastic or rubber, to reduce heat loss to the tissues in contact with it, between the connector 48 and outlet 50 or at least the most proximal cuff 42. Alternatively, effective thermal insulation can be achieved by proper selection of the catheter material itself and its channel wall thicknesses. To minimize diameter and maximize flexibility, the conduit 34 is typically extruded to have the gas ventilation channel 52, the fluid channels 44 and 46, and the liquid passageway 51 integrally formed therein. The above elements may alternatively be separately formed and bound in a common sheath (not shown), although this may disadvantageously affect the diameter and flexibility of the conduit 20.

The cuffs 40 and 42 are preferably constructed of polyurethane or other distensible material that will maintain structural integrity when stretched and yet not lose elasticity when subjected to high temperature liquids. The cuffs 40 and 42 are concentrically formed about the conduit 34 to be selectively inflated and deflated via liquids such as physiological saline or perfluorocarbon liquids, or gas such as air, through the channels 44 and 46. A suitable connector 62, such as a Leur lock fitting, is located at the terminal end of each channel 44 and 46 to provide attachment to a source of liquid or gas such as a lockable syringe or a hand or mechanical pump. In the circumstance whereby liquid is the preferred cuff inflation fluid, it is likely that some liquid will have been placed in the cuff prior to use, to insure a gas-free volume inside the cuff. When inflated, the cuffs 40 and 42 bear against the encircling inner walls of the trachea 28, bronchus 30, and/or lobar or segmented bronchus 32 (depending upon the positioned location of catheter 20 in the pulmonary air passages 22), in order to locally seal the lumen (3) of the airway(s) to prevent the passage of liquid and gas during the hyperthermic treatment. Although a pair of cuffs 40 and 42 are shown, one or both may be eliminated, e.g., if both lungs are to be filled with the fluid. Additional cuffs may also be used to provide the requisite sealing. The number of

cuffs used will depend on where the hyperthermic treatment is being directed in the lung, the passageways to be isolated and those to be kept gas ventilated, and the length of the catheter 20. In this regard, the cuffs 40 and 42, when required, are sized according to their application, i.e., whether they will be positioned in a large lobar bronchus (0.83 cm average diameter) or in a smaller segmental bronchus (0.56 cm average diameter). Cuffs sized to dam the main bronchi (1.22 cm average diameter) and trachea (1.8 cm average diameter) can also be readily fabricated. The use of two cuffs 40 and 42 in FIGURE 1 is for illustration purposes only and is not meant to imply that the untreated distal pulmonary segments 32 are to be unventilated by gas. In use, the catheter configuration(s) will be selected to reflect the requirement to gas ventilate untreated, air-filled portions of the lung.

The gas ventilation channel 52 is used to provide respiratory gas exchange to the portions of the lungs 24 not sealed off by the cuffs 40 and 42 or filled with the liquid. The channel 52 is preferably coupled to an appropriate machine, such as a mechanical ventilator, to supply gas through the port 53 formed in the wall of the conduit 34. In the absence of such a connection air ventilation may occur by the gas being drawn into channel 52 from room air by the natural respiratory motion of the lung.

The liquid connector 48 is attached to a liquid infusion system, such as described below. Briefly, such a system provides liquid for the desired treatment at a controlled but variable tidal volume and frequency, and at a controlled temperature and gas content. The pressure sensor 54 and the temperature sensor 56 positioned at the delivery end 36 permit monitoring of the temperature and pressure of the liquid within the liquid filled air passages. Additional sensors may be positioned at any point along the conduit 34 to permit comparative measurements and to permit flow rate information in the catheter to be obtained from dynamic measurements.

In use, the catheter 20 may be fitted with a rod (not shown) formed of bendable material, such as aluminum, that is bent, prior to insertion in most cases, to a configuration designed to guide the catheter 20 through the trachea 28 to the desired location in the pulmonary air passageways 20. A fiber-optic assembly may be used either alone or in conjunction with the rod to provide visual confirmation of the positioning of the catheter 10. Such a fiber-optic assembly, including an optical fiber having a lens, may be integrated into or associated with the catheter 20, and coupled to a light source and an eyepiece to permit observation via video camera, still photographs, or the eye. A fiber-optic bronchoscope may

be alternatively inserted through liquid passageway 51 for the same purpose. To assist in measuring distances to various parts of the lung, the outer surface of catheter 20 may be provided with distance indicator marks in spaced array.

Once the catheter 20 is in position, the various connectors at the proximal end are connected to the appropriate machines and monitoring devices. For instance, the liquid inlet/outlet connector 48 is attached to a liquid infusion system, and the fluid line connectors 62 are attached to suitable sources of liquid or gas. The cuffs 40 and 42 are inflated as necessary to seal off the pulmonary air passages adjoining the cancer cells while maintaining gas communication to untreated lung volume. The gas ventilation channel 52 is hooked to a mechanical ventilator and a suitable gas mixture is supplied through the port 53 to the unaffected air passageways. With temperature and pressure being monitored, liquid from the infusion system is supplied through the liquid passageway 51 to the, in this instance, bronchiole 32 at a controlled frequency and tidal volume (indicated by arrow 51). Following the hyperthermic treatment, the liquid can be removed from the pulmonary passages 20 by suction, by gravity (i.e., placing the patient tilted with the head down in the so-called "Trendelenburg" posture), and by evaporation.

The liquid infusion and isolation catheter 20 may also be used in conjunction with external intercostal ultrasound applicators to provide the means for liquid filling and to provide additional heating and/or cooling to the tumor site. For instance, as shown in FIGURE 2, a pair of intercostal applicators 66 and 68 are placed externally on the patient to direct sound waves between the ribs 70 and into the peripheral portions and bronchial spaces of the lung 24. These ultrasound power applicators 66 and 68 are composed of long aspect-ratio rectangular transducers 74, operated either singly or as a synchronous or asynchronous pairs. These applicators 66 and 68 can have flat (plane wave), broad-band unfocused transducers 74 or may have curved, focused transducers. Ideally these will be operated in the range from 250 KHz to 1 MHz.

Such applicators 66 and 68 can be used in conjunction with a liquid infusion and isolation catheter 20 to apply heat both convectively and ultrasonically to a specific portion of the lung 24. Although it would appear that a venetian blind or striped pattern of heating would result from this arrangement, it should be noted that the targeted tissue can be "scanned" up and down in front of the transducer array by a cyclic variation of the inflation pressure of the lung 24. This induced variation may be large or small, according to the motion desired. Likewise, the overall position of the tumor to be treated may be located with respect to the

applicators 66 and 68 by virtue of inflation or deflation of the lung 24. Also, the respiratory motion normally present in the lung 24 may be suppressed by imposing a constant liquid infusion pressure at the desired level. Although not shown, it is to be understood that the applicators 66 and 68 may be in fixed position relative to each other, such as by mounting to a jig or frame.

Although not shown in this view, a transducer can alternatively be applied directly to the body of the lung following surgical resection of a rib or other interfering tissues. The transducer for this application will typically be supplied with a bolus of degassed coupling liquid, also serving the function of cooling the transducer and tissue surfaces.

Another method of providing ultrasound hyperthermia is to place an ultrasound applicator within the fluid-filled pulmonary air passage near the tumor to be treated. FIGURE 3 shows a representative embodiment of such an intracavitary applicator 76 for delivering an ultrasound transducer 78 to the treatment site. To facilitate the description, the reference numbers used in FIGURE 1 are correspondingly employed in FIGURE 3 (and in FIGURE 4, described below). The intracavitary applicator 76 of FIGURE 3 includes a conduit 80 having a distal end 82 positionable within the pulmonary air passages 22 and a proximal end 84 that remains outside the thoracic air passage 22. The conduit 80 encases a ventilation passageway 86 passing through the transducer 78 in fluid communication with the pulmonary air passages 22 through a distal opening 88. The passageway 86 terminates at the proximal end 84 of the conduit 80 with a coupling 90 for attachment to a respirator (not shown). The conduit 80 also houses a liquid inlet port 92, typically positioned distal to the transducer 78, and a liquid return port 94 positioned, in this instance, proximal to the transducer 78. The liquid inlet port 92 is in fluid communication with a liquid inlet coupler 96, and a liquid return port 94 is in fluid communication with a liquid return coupler 98, both couplers 96 and 98 being located at the proximal end 84 of the conduit 80. Formed concentrically about the ventilation passageway 86 and positioned distal to the transducer 78 and liquid ports 92 and 94 is an inflatable cuff 100. A fluid line coupling 102 is in fluid communication with the cuff 100, for connecting the cuff 100 to a suitable source of pressurized liquid or gas (e.g., air). Power cables 104 pass through the conduit 80 to provide high frequency electrical power to the transducer 78.

This conduit 80 is constructed with similar materials and by similar methods as the liquid infusion catheter 20 described above. Here, in FIGURE 3, the transducer assembly 78 is positioned concentrically around the ventilation

passageway 86. In this manner, the distal cuff 100, when inflated, serves to dam the proximal pulmonary passages 30'. The distal cuff 100 also anchors the distal end 82 of the conduit 80, and thereby permits the transducer 78 to be manipulated into position in the center of the bronchus 30 (or trachea 28) to avoid contact with the bronchus wall 106 and the tumor 108. The cuff 100 is otherwise substantially the same as the cuffs 40 and 42 described above with respect to FIGURE 1. When the cuff 100 is inflated, it seals off the bronchus 30 so that a degassed liquid propagating medium 110 can be supplied to and fill the bronchus 30 through the liquid inlet port 92, to provide acoustic coupling and secondarily to cool the transducer assembly 78. Circulation of the liquid 110 may be accomplished by circulating liquid from the bronchus 30 through the liquid return port 94 to a liquid supply system, such as described below.

In order to prevent filling of the other lung, if that is desirable, an optional cuff plug 112, which is independent of the intracavitary transducer and its support shaft and conduit 80, is inserted within the other bronchus 30', and its degree of distension is controlled with pressurized liquid or gas supplied through a line 114. Respiration is accomplished through the one lung by supplying air through the ventilation passageway 86. Although not shown, it is to be understood that the cuff assembly 112 and 114 may, and preferably should, be supplied with a separate ventilation passageway (not shown) in order to ventilate the pulmonary air passage 32 distal to cuff plug 112. Pressure and temperature sensors (not shown) may also be disposed and used as desired, such as described above with respect to FIGURE 1. Installation of the intracavitary applicator 76 can be accomplished substantially the same way as described above with respect to the liquid infusion and isolation catheter 20. Positioning of the transducer 78 with respect to the tumor 108 is accomplished by rotating the conduit 80 as shown by the rotational arrow 116.

The construction of such a representative intracavitary transducer assembly 78 is shown in greater detail in FIGURE 4. Here, one approach to providing selective directional heating patterns is illustrated. FIGURE 4 shows a thin-walled piezoelectric ceramic cylinder 180 that is longitudinally and circumferentially sectioned into four separate power transducers, with transducers 120 and 122 formed to have an arcuate cross-sectional shape of approximately 120°, as indicated by angle θ; and with transducers 124 and 126 formed to have an arcuate cross-sectional shape with an included angle of approximately 240°, as represented by angle ϕ. Leads 128 supply power to the transducers, and the ventilation passageway 86 is shown, in this instance, passing coaxially through the

cylinder 180. This multiple-transducer approach provides flexible heating patterns. For instance, with transducers 120 and 122 driven in parallel, a 120° pattern can be achieved. Similarly, with transducers 124 and 126 driven in parallel, a 240° heating pattern can be achieved. Finally, with all of the transducers being driven together, a full 360° of heating can be achieved along the length of the cylinder 180. Of course, full 360° heating patterns may also be achieved by cylindrical piezoelectric cylinders that are not sectioned.

Although the transducer assembly 78 is shown mounted coaxial with the conduit 80, it is to be understood that other positions and transducer configurations can be used. For instance, transducers formed of flat plates may be associated with or placed adjacent to the conduit 80 to radiate sound waves in one or more directions. Likewise, the transducers 124 and 126 may be eliminated to leave only the transducers 120 and 122 mounted adjacent the conduit 80.

FIGURE 5 illustrates yet another representative embodiment of an intracavitary ultrasound applicator 130, in which a transducer assembly 132 positioned within a self-contained liquid-filled sac 134 for acoustic coupling and cooling. This applicator 130 includes a conduit 136 having a distal end 142 positioned within the bronchus 30 and a proximal end 144 positioned outside of the patient's body. A ventilation passageway 138 is formed within or associated with the conduit 130 having a ventilation port 140 formed approximately midway down the conduit 136 and an air line coupling 146 located at the proximal end 144 for attachment to a respirator (not shown). While not shown in this view, a ventilation passageway can also be provided to the distal end 142 if desired.

The conduit 136 also houses one or more liquid passageways that supply liquid from a liquid inlet coupling 148 to the distensible sac 134, and circulate liquid back to a liquid outlet coupling 150. The couplings 148 and 150 may be connected to a self-contained liquid supply system or a larger system containing a separate power supply circuitry and fluid flow module that circulates a degassed liquid at a controlled temperature for cooling the transducer assembly 132 and providing an acoustic coupling between the transducer assembly 132 and the pulmonary tissues and tumor 152. It is also possible to derive the coupling/cooling fluid from the liquid infusion system that supplies liquids to the lung. The sac 134 is constructed of a thin, pliable material, such as polyurethane, that readily conforms to the shape of an abutting pulmonary tissue or tumor to facilitate heating of the tumor. A fiber-optic assembly is shown as part of the applicator 130 having one or more optical fibers (not shown) passing through the liquid sac 134 and the transducer 132. The fiber-optic assembly includes a

lens 156 positioned on the distal end 142 of the conduit 136, an optical coupler 158 at the proximal end 144 to facilitate viewing through the lens 156 as previously described, and a light source that is supplied through cables 160 that also include power cables for the transducer assembly 132. A cuff 162 typically is formed on the conduit 80 distal to the transducer assembly 132, to be inflated and deflated through a cuff fluid line coupling 164 that is connected to a source of pressurized liquid or gas. This cuff 162 serves primarily an anchoring function, to assist and maintain acoustical positioning of the transducer 132 and liquid-filled sac 134 at the tumor site 152.

Both of the intracavitary applicators 76 and 130 described above can be positioned in the bronchial tree by first locating the tumor target via a flexible bronchoscope that indexes the lengths of the passageways and the position of the tumor. The applicator is then guided down the airways with the aid of a bendable rod, as described above. Such a rod is first bent slightly and then fed down one of the inner passageways of the applicator. The bend of the rod is sufficient to bend the distal end of the applicator in the desired direction. Supplementing this steering approach is a system of fiduciary marks taken from or correlated with the bronchoscope traversal that establishes the length required to descend down the airways. Finally, the fiber-optic assembly 154 can be used alone or in conjunction with the rod to accurately position the transducer assembly adjacent to the tumor to be treated.

The intracavitary applicator 130 may also be configured for hyperthermic treatment in other body cavities, e.g., the mouth, esophagus, uterus, or rectum, in which case a cuff may be provided for auxiliary anchoring purposes.

FIGURE 6 illustrates in greater detail a representative transducer assembly 132 for use in conjunction with the distensible acoustic-coupling sac 134. Here, the conduit 136 is shown in cross section having a liquid inlet passageway 166 centrally positioned within a concentric liquid return passageway 168. The liquid 170 passes through a manifold 172 into the lumen of the sac 134 to distend the sac 134 and circulate around the transducers 174. The liquid 170 then passes through the manifold 172 and into the return passageway 168. The circulation of the liquid 170, which is normally degassed water, aids in cooling the transducers 174 and provides an acoustic coupling for the ultrasound waves 176. Although not shown, it is to be understood that cuff fluid lines and the fiber-optic assembly lines can be constructed to pass axially through the sac 134 and the transducers 174 to distal positions along the conduit 136.

The invention is further illustrated by the following representative examples.

EXAMPLES

Based on the well-established biocompatibility of perfluorocarbon liquids, the issues most central to determining the feasibility of the disclosed convection and ultrasound hyperthermia techniques were those having to do with the fluid, thermal, and acoustic characteristics of perfluorocarbon liquids and lungs filled with perfluorocarbon liquids. Below, the general physical, thermal, and acoustic properties of candidate liquids are quantified in parameter ranges appropriate to lung heating, as confirmed by isolated lung and *in vivo* experiments. By employing perfluorocarbon liquids that meet the disclosed criteria, we have demonstrated sustained and controlled convective and ultrasound hyperthermia in large animal lungs *in vivo*.

A thorough investigation of the requisite properties of candidate perfluorocarbon liquids was undertaken. From these studies, the most suitable class of liquids was selected for use in confirming animal research. As described below, perfluorocarbon liquids were found to exhibit interesting acoustic properties leading to unexpected but, for the most part, favorable behavior for the purpose of liquid-filled lung ultrasound hyperthermia (LLUH). Chief among the findings are: a) pure perfluorocarbon liquids show measurable nonlinear acoustical behavior in intensity ranges suitable to LLUH (< 2 W/cm^2 @ 1 MHz), i.e., attenuation increases with power as well as frequency; and b) perfluorocarbons in the lung exhibit significant acoustical scattering of the ultrasound beam. The implications these observations have on the LLUH devices include 1) the need for lower frequencies than are used in conventional superficial ultrasound hyperthermia, 2) a natural advantage exists whereby inherent acoustic beam profile "smoothing" (i.e., flattening of the nearfield diffraction peaks) occurs due to augmented scattering, and 3) a potential benefit favoring focused ultrasound devices may exist in that preferential absorption in their focal regions should result from the nonlinear properties of these particular liquids. In addition, the physical properties of perfluorocarbon liquids have yielded some unexpected advantages. Chief among these are a) the tremendous gas solubility of the liquids make them unique in their ability to quickly and completely fill lung tissue, an advantage important for acoustic coupling, and b) the high gas solubility can likely be exploited to suppress cavitation in the liquid. In addition, the low surface tensions of perfluorocarbon liquids, as shown in FIGURE 8, enhance the liquids' ability to readily fill the lung. Also, when a lung becomes filled with liquid, liquid resides on both sides of the vascular spaces, that is, on both the gas side and the

blood side. By regulating the amount of liquid infused into the lung space, the blood flow can be controlled. This is because the more fluid that is introduced, the more compressed the lung capillaries become. Reduced blood flow is an important mechanism to reduce heat dissipation and therefore to further localize the treatment to the desired target tissues. Also, the liquid distribution in the lung can be used to control the distribution of pulmonary blood flow.

A wide range of perfluorocarbon liquids were initially considered in an evaluation of physical, thermal, and acoustic properties for selecting the most apt liquids for liquid-filled lung procedures. A summary of these properties is described in detail below.

EXAMPLE 1

General Characteristics of Perfluorocarbon Liquids

Physical properties: The candidate perfluorocarbon liquids spanned a wide range of molecular weights, as indicated in FIGURE 7. For reference purposes, the physical properties of the liquids are presented in the FIGURES in order of molecular weight, with water properties included for comparison, and, unless otherwise stated, are measured at 25°C.

Fluid flow properties: The predominant force involved in lung inflation is the surface force along alveolar walls due to the action of surface tension effects from the moist lining of the alveoli. The introduction of bulk liquid into the lung significantly reduces these forces since the gas/liquid interface is removed. Further reducing these forces is the fact that perfluorocarbon liquids have some of the lowest surface tensions recorded for liquids (FIGURE 8). These combined effects means that the net pressure to maintain inflation in a PFC-filled lung is roughly 20-30% of that required for air inflation [61]. This fact is advantageous for providing cuff isolation of lung lobes and segments since cuff sealing in the airways can be accomplished with lower pressures than for normal clinical bronchial intubation.

Perfluorocarbon liquids are generally poor solvents, being essentially insoluble in water, alcohols, and most biological materials. This is a primary key as to why they are superior to saline as acoustic coupling/heat transfer fluids for liquid-filled lung ultrasound and convection hyperthermia treatments. This immiscibility ensures that the phospholipid surfactant (which maintains low surface tension in alveolar wall moisture) will not readily be washed out of the treated lung. This in turn minimizes the respiratory difficulty which might otherwise occur in a lung after returning to gas ventilation [62].

To reduce liquid flow resistance into and out of the lung it is important to minimize the effects of viscous resistance. FIGURE 9 shows that some of the perfluorocarbon liquids considered are relatively high in absolute viscosity, compared to water. On this basis, liquids with molecular weights (see FIGURE 7 for molecular weights) higher than F-Decalin (i.e., perfluorodecalin) become less desirable. Strictly considered, flow resistance is more closely related to the "kinematic viscosity" (absolute viscosity/density) than absolute viscosity, usually as expressed in the "Reynolds Number" [63]. Considering the higher densities of the liquids (FIGURE 10), it is found that those perfluorocarbon fluids with molecular weights below F-Decalin have flow resistance characteristics equivalent to or better than water.

Gas solubility: To illustrate the tremendous capability of perfluorocarbon liquids to absorb dissolved gases, FIGURE 11 shows the oxygen solubility of six perfluorocarbon liquids in comparison with water. From the standpoint of exploiting this property to suppress cavitation, to assist in lung filling, and, of course, to enable simultaneous lung ventilation during liquid-filled lung hyperthermic treatments (via ultrasound and/or convection), the perfluorocarbon fluids are all roughly equivalent, with a slight preference going to molecular weights below F-Decalin.

EXAMPLE 2

Thermal Properties of Perfluorocarbon Liquids

Thermodynamic properties: In ultrasound lung heating it will be undesirable to induce boiling in the coupling liquid since, at the very least, this will interrupt acoustic coupling. As shown in FIGURE 12, this criterion renders FC-72 a very poor liquid selection, and RM-82 and FC-84 less than optimum as well. In this category, RM-101 and FC-75 roughly match the boiling points of tissues, so they are acceptable, though not as appealing as the higher molecular weight fluids.

The efficient removal of perfluorocarbon liquid from the lung after liquid-filled lung hyperthermia treatments must be a leading consideration in designing the proposed therapies. The primary removal mechanisms for the bulk liquid will be first pumping or suctioning the fluid from the lung, permissibly followed by gravity-induced drainage (enhanced by the high densities of perfluorocarbons). The remainder of the fluid is then removed by evaporation. The facility with which a liquid evaporates is expressed by its vapor pressure; the higher the value, the more rapid the evaporation. As FIGURE 13 demonstrates, perfluorocarbon liquids with molecular weights above F-Decalin are clearly unacceptable from this standpoint. It is not surprising that the most favorable liquids in this category

and blood pressure measurements. Additional surgical procedures during *in vivo* experiments included double or triple rib resections, to expose an acoustic window for the ultrasound applicator. Also, small needle thermometry probes were inserted in deep muscle and in the isolated region of the lungs (described below). All animals were euthanized with magnesium chloride.

Liquid-filled lung procedures: To quantify acoustic properties in perfluorocarbon-filled lungs *in vitro*, a series of experiments were performed on isolated adult sheep lungs. There is a striking visual difference between a normal air-filled lung and one which is filled with fluorocarbon liquid. The glistening dark red color characteristic of the successfully filled "liquid lung" was one measure of a lung reaching complete filling. In addition, measurements of acoustic propagation were also used to confirm the degree of filling. It was found, both in the *in vitro* and *in vivo* cases, that the lung filling process could be accomplished in about one-quarter of the time previously required for perfluorocarbons if the liquid were completely degassed prior to the initial infusion (only 1-3 minutes). The enhanced filling process was due to the perfluorocarbons' ability to dissolve great quantities of gas, rather than simply depend on displacing the trapped alveolar air. It was found that saline filling required much more time than for the fluorocarbons using partially degassed liquids.

In vitro ultrasound experimental materials and methods: *In vitro* ultrasound characterizations were performed with an applicator consisting of a narrow band 1.0-MHz, 6-cm piezo-ceramic disk transducer with temperature controlled coolant/coupling liquid continuously surrounding it. The system was capable of delivering 150 Watts of acoustic power, though these power levels were in excess of that required for fast warmup and certainly much more than was required for stable steady state lung hyperthermia.

The isolated lungs were instrumented either with thermocouple probes (29 gauge) or with ultrasound hydrophones for thermal or acoustic determinations of attenuation, respectively. Acoustic gel was used to insure good coupling into the tissue. The thermal technique used was that of determining the Specific Absorption Rate (SAR) from the initial rate of temperature rise [66] at different depths in the lung. Ratios of SAR at the various depths yielded attenuation. The hydrophone measurements recorded dynamic pressure variations directly which were displayed on an oscilloscope. Squaring of the pressure data resulted in data proportional to intensity, which could then be translated to attenuation values for known acoustic path lengths.

In vivo liquid-lung ultrasound hyperthermia materials and methods: To provide efficient filling of the lung lobe, completely degassed FC-75 was introduced through a conventional clinical bifurcated bronchial catheter that permitted infusion of the selected lung lobe while sustaining gas ventilation in the remainder of the lung. The catheter was placed without benefit of a bronchoscope, so the correct placement had to be determined by verification of lung inflation motions in the desired lung segments. The perfluorocarbon liquid was introduced at room temperature and only infrequently circulated in and out. In most cases the cranial segment of the right apical lobe was chosen for selective heating, both in the ultrasound and the convective hyperthermia experiments. These segments had inflated volumes of approximately 250-300 ml. An "acoustic window" to the lung segment was obtained by resection of portions of three ribs essentially analogous to an intraoperative hyperthermia treatment. The treated lung segment was partially exteriorized through the "window" to enable invasive thermometry of the treated lung at different depths. The sound was propagated directly through coupling water and membrane into the lung. In most cases, the lung surface was cooled with 37°C coupling water.

In addition to heating data, *in vivo* acoustic measurements were also performed via the hydrophone method previously described. Continuous recording of relevant physiological parameters were performed throughout the experiments. These measurements included systolic and diastolic blood pressure (reduced to Mean Arterial Pressure), core temperature, heart rate, and respiration rate. Gas ventilation was maintained by a mechanical respirator. Cardiopulmonary stability was confirmed throughout the treatments by taking periodic blood samples for arterial pH, pO_2, and pCO_2.

In vitro ultrasound results: FIGURE 26 presents typical *in vitro* attenuation values for isolated lung of an adult sheep. The attenuation shows a significant increase with increasing frequency. Note also that the attenuation levels are higher in the liquid-filled lung than for the pure liquid. It is postulated that this augmented attenuation is mostly attributable to scattering from the refraction effects of the sound speed mismatch between the parenchymal tissue and the liquid (increased scattering is supported by the ultrasound imaging results as well). Because scattering increases the effective acoustic path length, a wave traverses and spreads the beam slightly, the near loss-free propagation for lower frequencies (e.g., 250 and 500 KHz; FIGURES 20, 21, and 23) in perfluorocarbon liquids is no doubt preferred to frequencies above 1 MHz for deeper hyperthermia. Lower frequency ultrasound should also exhibit significantly

reduced scattering since the wavelength increases substantially (e.g., to 3-6 mm) in relation to the main scattering structures (i.e., bronchioles, diameters < 1 mm [56]).

FIGURE 27 demonstrates that the liquid-filled lung acoustic properties are dominated by the presence of the liquid (this likely also holds true for the thermal properties). This data shows that the effective sound speeds measured (both *in vivo* and *in vitro*) are close to those of the pure liquid (dashed line). Note that connective tissue sound speeds are usually higher than those of blood and muscle.

EXAMPLE 6

In Vivo Acoustic Lung Hyperthermia

Employing the methods and protocols described in Example 5, sustained hyperthermia (42-45°C to about 4 cm depth for 30 minutes) was successfully accomplished in the two animals used for the tests. The temperature vs. depth histories which resulted are represented by FIGURE 28, which depicts the experiment employing the greatest number of temperature probes. In this case probes were located in the interstitial tissue along the beam central axis at depths of 0.5, 1.0, and 2.0 cm, and also at 3.0 cm but slightly off axis. In addition, an on-axis probe was placed on the distal surface of the lung segment (approximately 6 cm from the treatment surface) between the lung surface and a rubber mat (which also acted as an acoustic absorber). As shown, lung temperatures exceeded 43°C to approximately 3 cm depth, with acoustic penetration through the lung segment indicated by the high temperatures on the distal surface (effectively 6 cm deep). The close tracking of the 2 and 3 cm depth temperatures (again, not in line with each other) may have been due to refractive effects or differences in local perfusion. The lower temperature at the 0.5 cm site is due to the conductive cooling of the coupling water (at 37°C). The "thoracic cavity" core temperature probe was located near the treated segment in the cavity. The steady state power requirements in this case ranged between 12 to 15 Watts, again indicative of low pulmonary perfusions due to the liquid presence.

Perfusion response of the liquid-filled lung: The ultrasound power levels required for steady state hyperthermia were unexpectedly low due to low blood flow levels in the heated lung. An analysis of the physiological mechanisms involved, however, indicates that the perfusion is suppressed due to the combined effects of: 1) increased pulmonary vascular resistance due to the presence of the liquid compressing alveolar capillaries, 2) the shunting of the pulmonary circulation to other areas of the lung from locally low pO_2 (here from degassed liquids), and 3) to shunting from a low pH buildup in the lobe [29,30,31].

EXAMPLE 7

In Vivo Convective Lung Hyperthermia

Convection hyperthermia materials and methods: Using the large animal liquid ventilation (LALV) system of Temple University (FIGURE 29), heated, temperature-controlled FC-75 could be circulated in and out of lung lobes and segments isolated via the bifurcated bronchial catheter method as described above. The animal preparation was essentially the same as for the ultrasound experiments. In this way convective lung hyperthermia was successfully administered to the cranial segment of the right apical lung lobe. To instrument the lung so that temperature probes could be easily placed at known depths, the lung segment was partially exteriorized through a "window" created in the same manner as was done for the ultrasound experiments.

FIGURE 30 shows the temperature history data for the convective lung hyperthermia experiment. The setup period was used for establishing proper placement and sealing of the liquid delivery catheter, for proper temperature probe placement, and to assess the response of the lung to LLCH parameter changes. It was found that the very thin wall (≈ 2 mil) vinyl air cuffs on the available bifurcated catheters had very little structural integrity at the elevated liquid temperatures required of the hyperthermic treatment. As such, the catheters provided adequate, but not high quality, sealing. Although this had very little physiological impact (since the gas ventilation of the remaining lung was quite adequate), it did result in diminished heat transfer rates. The development of a suitable liquid delivery catheter was therefore mandated.

During the experiment, the heat transfer to the lung segment was varied by changing both the inspiratory liquid temperature (T_{ins}) and the tidal volume (V_t) under constant cycling (5 "breaths" per minute) conditions. Beginning with a low T_{ins}, low V_t condition (43°C, 40 ml), it was found that temperatures in the therapeutic range slowly fell below hyperthermic values. Lung perfusion effectively cooled the lung under these conditions. However, increases in T_{ins} and V_t overcame this decline, bringing temperatures back up above 45°C (t = 60 minutes). Once the lung has reached the desired therapeutic temperature, the T_{ins} and V_t settings were adjusted downward to maintain good steady state hyperthermia (t > 60 min).

Noteworthy trends: First, the temperature probes in the center of the lung segment interstitium (spaced 2-3 cm apart) consistently were within 0.5°C of each other at the higher tidal flows (t > 60 min), and were usually within 1°C of each other at the lower flows (t < 40 min). Therefore, spatially uniform heating can

readily be achieved and controlled via the tidal flow. Secondly, the rates of lung temperature increase shown during the experiment (≈ 0.25 C/min) are much more sluggish than rates which should occur at similar T_{ins} values in a properly designed clinical device. This is due to the aforementioned compromised heat transfer from the leaky catheter cuff. Indeed, much higher rates were found during the setup period prior to cuff leakage (≈ 1 C/min for t < 25 min). Lastly, it should be noted that steady state lung temperatures closely tracked T_{ins}, which was measured outside the animal in the liquid circuit. By placing a temperature sensor at the distal end of the catheter, at the entrance to the heated lung lobe or segment, the lung temperatures should be known with a high degree of certainty. This is significant in that there should be no need for invasive lung thermometry during the subject treatment

EXAMPLE 8

Ultrasound Imaging for Liquid-filled Lung Procedures

The presence of liquid in the lung theoretically makes possible the use of ultrasound imaging, both for viewing lung structures and for use in conjunction with the ultrasound and convection treatments. Both *in vitro* and *in vivo* ultrasound imaging experiments were performed on perfluorocarbon-filled lungs as part of the animal studies described above. The diagnostic imaging system was a commercial clinical system (Diasonics) capable of sector-scanned images at frequencies from 3 to 7 MHz. B-scan images were obtained on exteriorized perfluorocarbon-filled lung lobes and on lung lobes viewed through the rib cage and intrathoracically.

Consistent with the ultrasound results discussed previously, it was found that the increased attenuation and scattering of the very high diagnostic frequencies (3-7 MHz) rendered the diagnostic value of imaging deep lung structures through liquid-filled lung parenchyma poor. The imaging of structures through liquid-filled lung parenchyma may be the one area where saline-filling of lungs provides a distinct advantage (due to matched sound speeds).

The foremost advantages of diagnostic ultrasound imaging in the present application are for monitoring the lung-filling process and for confirming the integrity of the acoustic path. This conclusion is based on the distinct ultrasound images which were obtained when lung lobes reached gas-free or near-gas-free states.

EXAMPLE 9

Liquid-Filled Lung Hyperthermia and Chemotherapy

The prospects for using perfluorocarbon liquids as drug delivery vehicles may be quite favorable since commercial examples of fluoropharmaceuticals are many and diverse [60]. In addition, simultaneous locally delivered anesthesia in the treated tissue should also be possible via liquid delivery (though systemic anesthetic effects may also result). Although anesthetic use is often contraindicated in hyperthermia for safety reasons, because the maximum temperature in the lung may be set by the clinician with confidence in the subject (especially convection) treatments, simultaneous anesthesia may be feasible in this procedure. Coincidentally, fluorine-containing inhalation anesthetics account for the largest volume of fluorocompounds sold for purposes that are nonindustrial [60].

EXAMPLE 10

Ultrasound Intracavitary Applicator (ICA) Experiments

FIGURE 4 shows a schematic of a representative applicator head. A thin-walled piezoelectric ceramic cylinder (= 1.0 MHz resonance) was longitudinally and circumferentially sectioned into four separate power transducers with 120° and 240° included angles, respectively. The multiple-transducer approach provided flexible heating patterns. In these studies transducers 120 and 122 were driven in parallel (forming a synchronous pair), as were 124 and 126. Depending upon whether each pair or both were driven, either 120°, 240°, or a full 360° of heating could be achieved along the length of the cylinder. The transducers were mounted in an applicator with self-contained cooling and an integral water bolus for sound coupling, as depicted in FIGURE 6. The diameter of this first engineering prototype ICA transducer was 16 mm. Smaller cylinders more suitable for bronchial applications, however, can be readily made.

The applicator was mounted on a long (1 meter), flexible tubular shaft which housed the inlet and exit flow channels to the coupling bolus, as well as the RF power cables to the transducer. The water coolant flow dissipated heat to a maximum power of 100 Watts. The flow system was also characterized for pressure drop vs. flow rate to assure that acceptable pressure drops could be maintained in the long, narrow coolant channels.

The ultrasound beam quality was mapped in an acoustic test tank, while the thermal performance of the device was evaluated in a specially constructed body cavity phantom. FIGURE 31 shows the acoustic intensity mapped (via hydrophone) in water along the axial direction (z) of the transducer, 2 cm from the surface and

in the middle of the 240° arc of energized transducers 124 and 126. FIGURE 32 presents SAR patterns measured in tissue-equivalent cavity phantoms by needle thermocouple probes at five axial positions and several azimuthal angles (measured from the center of the 240° arc of transducers 124 and 126. FIGURE 33 shows the depth (radially outward) heating patterns in the phantom from the surface to 2 cm into the phantom tissue. The 100-Watt maximum power employed is more than will be needed for most applications.

EXAMPLE 11

Liquid-filled Lung Convection Hyperthermia (LLCH) System

FIGURE 34 schematically shows a representative LLCH system. The system is constructed under requirements applicable to clinical use. It is designed to maintain complete sterility of the liquids and catheters, and is modular and portable for convenient use in either a surgical theater or hyperthermia/oncology suite. The LLCH system provides heated, temperature-controlled perfluorocarbon liquid to the patient in either degassed or oxygenated form (partially degassed liquid states are also possible). To impose controlled lung temperatures and heat transfer rates, the tidal volume and "ventilation" frequency (cycling rate of the fluid into and out of the lung), and the input liquid temperature are controlled by the operator. To insure sterility, the unit employs roller-type peristaltic pumps which completely contain the liquid in sterile tubing. Similarly, valves, fluid fittings, and reservoirs are easily replaced and sterilizable, or disposable. The inspiratory and expiratory flows, system liquid temperatures and components status are monitored and controlled by a central computer. The computer serves as the operator console during treatment, recording and displaying LLCH system parameters and invasive temperature probe data, and is also a workstation for data playback and post-treatment analyses.

Conclusions

The foregoing research was highlighted by the first *in vivo* demonstrations of both acoustic and convective hyperthermia of the lung, here in a suitably large animal model. Controlled and sustained therapeutic temperatures were maintained with relatively few complications. These experiments, complemented by laboratory bench and *in vitro* acoustic measurements with perfluorocarbon liquids, identified the important clinical requirements for liquid-filled lung ultrasound and convection hyperthermia. Among these are a) lower ultrasound frequencies than traditionally used for soft tissue heating are required, b) traditional bifurcated bronchial catheters are inadequate, mainly due to their thin-walled air cuffs and lack of temperature and pressure instrumentation, and

c) the use of degassed perfluorocarbon liquids greatly facilitates the filling of lungs. Of tremendous practical significance are the observations that d) diagnostic ultrasound imaging can be very helpful in assessing the lung filling and the acoustic path available, and e) invasive thermometry will likely not be required for the convection hyperthermia treatments. Additionally, the fundamental fluid and thermal design ranges appropriate to the ultrasound treatment, including the range of inflation pressures, temperatures and tidal volumes, were determined.

Perfluorocarbon liquids have several unique properties. Measurable nonlinear acoustical behavior and scattering in the range of powers suitable to hyperthermia were found in laboratory and animal tests. While dictating the use of lower ultrasound frequencies, these characteristics can be advantageous for spatial smoothing of near field beam patterns and may be able to be exploited for their potential to produce localized enhanced absorption with focused ultrasound beams. In addition, the high gas solubility of perfluorocarbons should serve to suppress acoustic cavitation in the liquid by retarding rapid gas saturation.

The salient design requirements for clinical devices for 1) fluid processing and delivery systems suitable for liquid-filled lung hyperthermia procedures, 2) intracavitary ultrasound applicators for broncho-tracheal tumors, and 3) low-frequency external ultrasound applicators were also determined.

While representative and preferred embodiments of the invention have been described and illustrated, it is to be understood that, within the scope of the appended claims, various changes can be made therein. Hence, the invention can be practiced in ways other than those specifically described herein.

LITERATURE CITATIONS

1. Petrovich, Zbigniew: "Advances: Using Heat in Treatment of Some Cancers," article by Thomas C. Hayes, New York Times, Dec. 2, 1987.

2. Bleehan NM: Role of Hyperthermia in Treatment of Lung Cancer. Cancer Treatment Symposia, Vol. 2, Bleehan (Ed), p. 75, 1985.

3. Shaffer TH: A Brief Review: Liquid Ventilation, Undersea Biomedical Research, Vol. 14, No. 2, pp. 169-179, 1987.

4. Biro PB and Blais P: Perfluorocarbon Blood Substitutes. CRC Critical Reviews in Oncology/Hematology, Vol. 6, No. 4, pp. 311-374, 1987.

5a. Silverberg E and Lubera JA: Cancer Statistics, 1989. Ca - A Cancer Journal for Clinicians, Vol. 39, No. 1, pp. 3-20, 1989.

5b. Cancer Facts and Figures, 1987, p. 25. American Cancer Society, New York, N.Y., 1987.

6. Timothy AR: The Role of Radiotherapy in Carcinoma of the Bronchus. Bronchial Carcinoma, An Integrated Approach to Diagnosis and Management, p. 232-254, Springer-Verlag, New York, 1984.

7. Crawford S and Pierson D: Lung Cancer in "The Respiratory System," syllabus from University of Washington School of Medicine, pp. 240-249, 1985.

8. Kapp DS: Site and Disease Selection for Hyperthermia Trials. International Journal of Hyperthermia, Vol. 2, No. 2, pp. 139-156, 1986.

9. Karasawa K, Muta N, Takahashi N, Aoki Y, Nakagawa K, Sakata K, Akanuma A, Iio M: RF Capacitive Hyperthermia and Radiotherapy of Lung Cancer, presented at the 5th International Symposium on Hyperthermic Oncology, Kyoto, Japan, Aug. 29 - Sept. 3, 1988.

10. Makowski H, Tentchev P, Frey R, Necek S, Bergmann H and Blauhut B: Tolerance of an Oxygen-carrying Colloidal Plasma: Substitute in Human Beings. Fourth International Symposium on Perfluorochemical Whole Blood Substitutes, Kyoto Mitsuno T and Naito R, Excerpta Medica, Amsterdam, p. 47, 1979.

11. Maugh TH: Blood Substitute Passes its First Test, Science, Vol. 206, p. 205, 1979.

12. Mitsuno T, Tabuchi Y, Ohyanagi H and Sugiyama T: Further Studies on Intake and Retension of Fluosol-DA in RES in Humans. Advances in Blood Substitute Research, Bolin, Geyer and Nemo (Eds), Alan R. Liss, New York, p. 257, 1983.

13. Nishimura N and Sugi T: Changes of Hemodynamics and 02 Transport associated with the Perfluorochemical Blood Substitute Fluosol-DA. Critical Care Medicine, Vol. 12, p. 36, 1983.

14. Tremper KK and Cullen BF: U.S. Clinical Studies on the Treatment of Anemia with Fluosol-DA (20%). Artificial Organs, Vol. 8, p. 19, 1984.

15. Mitsuno T, Ohyanagi H and Naito R: Clinical Studies of a Perfluorochemical Whole Blood Substitute (Fluosol-DA): Summary of 186 Cases. Annals of Surgery, Vol. 195, p. 60, 1982.

16. Rude RE, Glogar D, Khuri SF, Kloner RA, Karaffa S, Muller JE, Clark LC and Braunwald E: Effects of Intravenous Fluorocarbons during and without Oxygen Enhancement on Acute Myocardial Ischemic Injury Assessed by Measurement of Intramyocardial Gas Tensions. American Heart Journal, Vol. 103, 986-995, 1982.

17. Ricci JL, Sloviter HA and Ziegler MM: Intestinal Ischemia: Reduction of Mortality Utilizing Intraluminal Perfluorochemical, American Journal of Surgery, Vol. 149, p. 84 1985.

18. Usui M, Sakata H and Ishii S: Effect of Fluorocarbon Perfusion upon the Preservation of Amputated Limbs, British Journal of Bone and Joint Surgery, Vol. 67, p. 473, 1985.

19. Clark LC: Theoretical and Practical Considerations of Fluorocarbon Emulsions in the Treatment of Shock. Chap. 37 in Pathophysiology of Shock, Anoxia and Ischemia, Cowley and Trump (Eds), Williams and Wilkins, pp. 507-521, 1982.

20. Klystra JA, Tissing MO, Ban der Maen A: Of Mice and Fish. Transactions of the American Society for Artificial Internal Organs, Vol. 8, pp. 378-383, 1962.

21. Reufer R: Surfactant and Alveolar Surface Forces after Breathing of an Inert Fluorinated Liquid, Federal Proceedings., Vol. 29, No. 5, pp. 1813-1815, 1970.

22. Clark LC and Gollan F: Survival of Mammals Breathing Organic Liquids Equilibrated with Oxygen at Atmospheric Pressure. Science, Vol. 152, pp. 1755-1756, 1966.

23. Modell JH, Newby EJ, and Ruiz BC: Long-term Survival of Dogs after Breathing Oxygenated Fluorocarbon Liquid, Federation Proceedings, Vol. 29, No. 5, pp. 1731-1739, 1970.

24. Modell JH, Calderwood HW, Ruiz BC, Tham MK and Hood CI: Liquid Ventilation of Primates. Chest, Vol. 69, pp. 79-81, 1976.

25. Calderwood HW, Ruiz BC, Tham MK, Modell JH and Hood CI: Residual Levels and Biochemical Changes after Ventilation with Perfluorinated Liquid. Journal of Applied Physiology, Vol. 139, pp. 603-607, 1975.

26. Forman D, Bhutani VK, Hilfer SR and Shaffer TH: A Fine Structure Study of the Liquid-Ventilated New Rabbit. Federation Proceedings Vol. 43, p. 647, 1984.

27. Rufer R and Spitzer L: Liquid Ventilation in the Respiratory Distress Syndrome. Chest, Vol. 66, July 1974 Supplement, pp. 29S-30S, 1974.

28. Puchetti V, Maffezzoli GF, Costa F, Montresor E, Sgro M, and Carolo F: Liquid Ventilation in Man: First Clinical Experiences on Pulmonary Unilateral Washing using Fluorocarbon Liquid. Fourth World Congress for Bronchology (Abstracts), p. 115, 1984.

29. Shaffer TH, Douglas PR, Lowe CA and Bhutani VK: The Effects of Liquid Ventilation on Cardiopulmonary Function in Preterm Lambs. Pediatric Research, Vol. 17, pp. 303-306, 1983.

30. Shaffer TH, Forman DL and Wilfson MR: Physiological Effects of Ventilation with Liquid Fluorocarbon at Controlled Temperatures. Undersea Biomedical Research, Vol. 11, No. 3, pp. 287-298, 1984.

31. Lowe CA and Shaffer TH: Increased Pulmonary Vascular Resistance during Liquid Ventilation. Undersea Biomedical Research, Vol. 8, No. 4, pp. 229-238, 1981.

32. Gollan F and Clark LC: Prevention of Bends by Breathing and Organic Liquid. Transactions of the Association American Physicians, Vol. 29, pp. 102-109, 1967.

33. Sass DJ, Ritman EL, Caskey PE, Bancers N, Wood EH: Liquid Breathing: Prevention of Pulmonary Arterio-Venous Shunting during Acceleration. Journal of Applied Physiology, Vol. 32, pp. 451-455, 1972.

34. Shaffer TH, Rubenstein D, Moskowitz GD, and Delivoria-Papadopoulos: Gaseous Exchange and Acid-base Balance in Premature Lambs During Liquid Ventilation Since Birth, Pediatric Research, Vol. 10, p. 227-231, 1976.

35. Wolfson MR, Tran N, Bhutani VK, and Shaffer TH: A New Experimental Approach for the Study of Cardiopulmonary Physiology During Early Development, Journal of Applied Physiology, Vol. 65, No. 3, pp. 1436-1443, 1988.

36. Shaffer TH, Tran HN, Bhutani VK, and Sivieri EM: Cardiopulmonary Function in Very Preterm Lambs During Liquid Ventilation. Pediatric Research, Vol. 17, pp. 680-684, 1983.

37. Shaffer TH, Delivoria-Papadopoulos M, Arcinue E, Paez P, and Dubois AB: Pulmonary Mechanics in Premature Lambs During the First Few Hours of Life. Respiratory Physiology, Vol. 28, pp. 179-188, 1976.

38. Shaffer TH, Douglas PR, Lowe CA, Bhutani VK: Liquid Ventilation: Improved Gas Exchange and Lung Compliance in Preterm Lambs. Pediatric Research, Vol. 17, pp. 303-306, 1983.

39. Shaffer TH: Personal communication, June 1989.

40. Neus E: Premature Infant Held to Life by Breathing Liquid. The Cincinnati Enquirer, p. D1, August 3, 1989.

41. Moskowitz GD and Greiner TJ: Heat Transfer During Liquid Breathing. Proceedings of 28th Conference on Engineering in Medicine and Biology, p. 17, 1975.

42. Forman DL, Bhutani VK, Tran N, and Shaffer TH: A New Approach to Induced Hypothermia. Journal of Surgical Research, Vol. 40, pp. 36-42, 1986.

43. Dawson CA, Johnston MR, Rickaby DA, and Fehring JF: The Influence of Hyperthermia on Isolated Perfused Lung. FASEB Journal, Vol. 3, No. 3, p. A546, 1989.

44. Teicher BA and Rose CM: Perfluorochemical Emulsion Can Increase Tumor Radiosensitivity, Science, Vol. 223, p. 934, 1984.

45. Teicher BA and Rose CM: Effects of Dose and Scheduling on Growth Delay of the Lewis Lung Carcinoma Produced by the Perfluorochemical Emulsion, Fluosol-DA, International Journal of Radiation Biology and Physics, Vol. 12, pp. 1311-1313, 1986.

46. Russell GE, Brass-Marlow EL, Nunno MP, Holst RJ, Waldow SM, Lustig RA, and Wallner PE: Response of Primary and Metastatic Lewis Lung Tumors to Fluosol-DA 20%, Oxygen and X-Radiation, presented at the Ninth Annual Meeting of the North American Hyperthermia Group, Seattle, Washington, March 18, 1989.

47. Rose CM, Lustig R, McIntosh N, and Teicher BA: A Clinical Trial of Fluosol DA 20% in Advanced Squamous Cell Carcinoma of the Head and Neck, International Journal of Radiation Biology and Physics, Vol. 12, pp. 1325-1327, 1986.

48. Ohyanagi H, Nishiijima M, Usami M, and Nishimatsu S: Experimental Studies on the Possible Combined Chemotherapy to Neoplasms with Fluosol-DA Infusion, in Advances in Blood Substitute Research, Bolin, Geyer, and Nemo (Eds.), Alan R. Liss, New York, p. 315, 1983.

49. Ref. 4 (Biro and Blais), p. 334.

50. Saunders MI: Hypoxic Cell Radiosensitization in Carcinoma of the Bronchus, in Cancer Treatment Symposia, Vol. 2, pp. 69-73, 1985.

51. Clark LC, Ackerman JL, Thomas SR, Millard RW, Hoffman RE, Pratt RG, Ragle-Cole H, Kinsey RA, and Janakiraman R: Perfluorinated Organic Liquids and Emulsions as Biocompatible NMR Imaging Agents for 19F and Dissolved Oxygen from Oxygen Transport to Tissue - VI, Bruley, Bicher and Reneau, Plenum, pp. 835-845, 1985.

52. Ackerman JL, Clark LC, Thomas SR, Pratt RG, Kinsey RA, Becattini F: NMR The[illegible]al Imaging, Proceedings of 3rd Annual Conference of the Society of Magnetic Resonance in Medicine, August 13, 1984, New York, New York,

53. Thomas SR, Clark LC, Ackerman JL, Pratt RG, Hoffman RE, Busse LJ, Kinsey RA, and Sumaratunga RC: MR Imaging of the Lung Using Liquid Perfluorocarbons. Journal of Computer Assisted Tomography, Vol. 10, No. 1, pp. 1-9, 1986.

54. Long DM, Mai-shian L, Szanto PS, Alrenga DP, Patel MM, Rios MV, and Nyhus LM: Efficacy and Toxicity Studies with Radiopaque Perfluorocarbon. Radiology, Vol. 105, pp. 323-332, 1972.

55. Church CC: A Theoretical Study of Cavitation Generated by An Extracorporeal Shock Wave Lithotripter. Journal of the Acoustical Society of America, Vol. 86, No. 1, pp. 215-227, 1989.

56. Comroe JH: Physiology of Respiration, 2nd Ed., Year Book Medical Publishers, pp. 118-119, 1974.

57. Sekins KM: An Oscillating Helix Artificial Lung Employing Oxygen-Perfused Inner Capillaries. Proceedings of the 30th Annual Conference on Engineering in Medicine and Biology, paper 35-9, 1977.

58. Kapp DS, Fessenden P, Cox RS, Bagshaw MA, Hahn GM, Fei-Fei L, Lee E, Prionas SD, and Lohrback A: Prognostic Factors Predicting Tumor Response (TR), Local Control (LC), and Complications (C) in Patients Treated on Randomized Protocols with Radiation Therapy (XRT) and Either 2 or 6 Hyperthermia Treatments (HT). Abstracts of Eighth Annual Meeting of the North American Hyperthermia Group, p. 20, 1988.

59. Haveman, J: "Enhancement of Radiation Effects by Hyperthermia," in Hyperthermia in Cancer Treatment, Vol. I, Anghileri and Robert (Eds.), pp. 171-172, CRC Press, Boca Raton, Florida, 1986.

60. Chase GD, Deno RA, Gennaro AR, Gibson MR, Stewart CK, King RE, Martin AN, Swinyard EA, VanMeter CT, Osol A, Witlin B, and Hoover JE: Remington's Pharmaceutical Sciences 14th Edition, Mack Publishing, Easton, PA, 1970.

61. Gollan F, McDermott J, Johnson AE, and Namon R: Compliance and Diffusion During Respiration with Fluorocarbon Fluid. Federal Proceedings, Vol. 29, No. 5, pp. 1725-1730, 1970.

62. Reufer R: Surfactant and Alveolar Surface Forces after Breathing of an Inert Fluorinated Liquid, Federal Proceedings, Vol. 29, No. 5, pp. 1813-1815, 1970.2. Olson RM: Essentials of Engineering Fluid Mechanics, 3rd Ed., Intext, New York, p. 336, 1973.

63. Olson RM: Essentials of Engineering Fluid Mechanics, 3rd Ed., Intext, New York, NY, p. 336, 1973.

64. Holman, JP: Heat Transfer, 4th Ed. McGraw-Hill, New York, p. 170, 1976.

65. Carson PL and Banjavec RA: Radiation Force Balance Systems for Precise Acoustic Power Measurement. AIPS document PAPS JASMA-70, American Institute of Physics, New York, NY, 1980.

66. Guy AW, Lehmann JF, and Stonebridge JB: Therapeutic Applications of Electromagnetic Power, IEEE Vol. 62, No. 1, pp. 59-60, 1974.

67. Keilman GK: New Ultrasound Hyperthermia Applicators with Improved Bandwidth and Spatial Uniformity. Abstracts of the 9th Annual Meeting of the North American Hyperthermia Group, p. 32, 1989.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A hyperthermic treatment of lung cancer, comprising the steps of:

temporarily filling with a liquid medium preselected pulmonary air passages adjoining pulmonary tissues comprising malignant cells,

circulating exogenously heated liquid medium having a temperature in the range of from about 41 to about 50°C through the liquid-filled pulmonary air passages for a period of time, and

thereafter removing the liquid medium from the pulmonary air passages of the patient.

2. The hyperthermic treatment of Claim 1, wherein the temperature is in the range of from about 42° to about 45°C.

3. The hyperthermic treatment of Claim 1, wherein the liquid medium is a perfluorocarbon liquid.

4. The hyperthermic treatment of Claim 3, wherein the perfluorocarbon liquid is characterized by an average molecular weight in the range of from about 350 to about 560.

5. The hyperthermic treatment of Claim 4, wherein the perfluorocarbon liquid is characterized by an average molecular weight in the range of from about 400 to about 460.

6. The hyperthermic treatment of Claim 5, wherein the perfluorocarbon liquid is characterized by an average molecular weight in the range of from about 420 to about 460.

7. The hyperthermic treatment of Claim 3, wherein the perfluorocarbon liquid is characterized by having:

viscosity less than about 5 CP at 25°C,

density less than about 2.0 g/cm^3 at 25°C,

boiling point greater than about 55°C,

vapor pressure in the range of from about 20 Torr to about 200 Torr, and

Prandtl number less than about 10 at 25°C.

8. The hyperthermic treatment of Claim 7, wherein the perfluorocarbon liquid is characterized by having a vapor pressure less than about 100 Torr.

9. The hyperthermic treatment of Claim 7, wherein the perfluorocarbon liquid is characterized by having O_2 solubility greater than about 40 ml/100 ml.

10. The hyperthermic treatment of Claim 4, wherein the perfluorocarbon liquid is selected from among FC-84, FC-72, RM-82, FC-75, RM-101, dimethyl-adamantane, trimethylbicyclononane, and perfluorodecalin.

11. The hyperthermic treatment of Claim 1, wherein the liquid medium is physiological saline.

12. The hyperthermic treatment of Claim 1, wherein the filling of the liquid-filled pulmonary air passages is monitored by diagnostic ultrasonic imaging.

13. The hyperthermic treatment of Claim 1, further comprising the step of irradiating the malignant cells with ionizing radiation.

14. The hyperthermic treatment of Claim 3, wherein the perfluorocarbon liquid is substantially degassed during the filling step.

15. The hyperthermic treatment of Claim 14, further comprising the step of oxygenating the liquid medium in the liquid-filled pulmonary air passages.

16. The hyperthermic treatment of Claim 1, wherein the preselected pulmonary air passages are filled with substantially degassed perfluorocarbon liquid, exogenously heated oxygenated perfluorocarbon liquid is circulated into and out of the liquid-filled pulmonary air passages, and the malignant cells are irradiated with ionizing radiation.

17. The hyperthermic treatment of Claim 1, wherein the liquid medium comprises a therapeutic agent.

18. The hyperthermic treatment of Claim 17, wherein the liquid medium is an aqueous perfluorocarbon liquid emulsion.

19. A hyperthermic treatment of lung cancer, comprising the steps of:

temporarily filling with a liquid medium preselected pulmonary air passages adjoining pulmonary tissues comprising malignant cells,

heating the adjoining pulmonary tissues comprising the malignant cells to a temperature in the range of from about 41° to about 50°C for a period of time by transmitting ultrasound through the liquid-filled pulmonary air passages, and

thereafter removing the liquid medium from the pulmonary air passages of the patient.

20. The hyperthermic treatment of Claim 19, wherein the temperature is in the range of from about 42° to about 45°C.

21. The hyperthermic treatment of Claim 19, wherein the liquid medium is a perfluorocarbon liquid.

22. The hyperthermic treatment of Claim 21, wherein the perfluorocarbon liquid is characterized by an average molecular weight in the range of from about 400 to about 500.

23. The hyperthermic treatment of Claim 22, wherein the perfluorocarbon liquid is characterized by an average molecular weight in the range of from about 400 to about 460.

24. The hyperthermic treatment of Claim 23, wherein the perfluorocarbon liquid is characterized by an average molecular weight in the range of from about 420 to about 460.

25. The hyperthermic treatment of Claim 21, wherein the perfluorocarbon liquid is characterized by having:

viscosity less than about 5 CP at 25°C ,

density at less than about 2.0 g/cm^3 at 25°C,

boiling point greater than about 75°C,

vapor pressure in the range of from about 25 Torr to about 100 Torr,

acoustic impedance in the range of from about 0.8 to about 1.6 MegaRayls at 37°C,

acoustic attenuation less than about 1.2 dB/cm at 1.0 MHz, 45°C, and an acoustic intensity of about 3 W/cm^2.

26. The hyperthermic treatment of Claim 25, wherein the perfluorocarbon liquid is characterized by O_2 solubility greater than about 40 ml/100 ml.

27. The hyperthermic treatment of Claim 23, wherein the perfluorocarbon liquid is selected from among FC-75, RM-101, and perfluorodecalin.

28. The hyperthermic treatment of Claim 21, wherein the ultrasound is in the frequency range of from about 250 KHz to about 3 MHz.

29. The hyperthermic treatment of Claim 28, wherein the ultrasound is in the frequency range of from about 500 KHz to about 2 MHz.

30. The hyperthermic treatment of Claim 28, wherein the ultrasound is in the frequency range of from about 250 KHz to about 1.5 MHz.

31. The hyperthermic treatment of Claim 19, wherein the liquid medium is physiological saline.

32. The hyperthermic treatment of Claim 31, wherein the ultrasound is in the frequency range of from about 250 KHz to about 3 MHz.

33. The hyperthermic treatment of Claim 32, wherein the ultrasound is in the frequency range of from about 500 KHz to about 3 MHz.

34. The hyperthermic treatment of Claim 33, wherein the ultrasound is in the frequency range of from about 750 KHz to about 3 MHz.

35. The hyperthermic treatment of Claim 19, wherein the ultrasound is produced by a transducer disposed within the liquid-filled pulmonary air passages.

36. The hyperthermic treatment of Claim 19, wherein the ultrasound is produced by a transducer disposed exogenous to the liquid-filled pulmonary air passages.

37. The hyperthermic treatment of Claim 36, wherein the ultrasound is transmitted through an intercostal space of the patient.

38. The hyperthermic treatment of Claim 19, wherein the filling of the liquid-filled pulmonary air passages is monitored by diagnostic ultrasonic imaging.

39. The hyperthermic treatment of Claim 21, wherein the perfluorocarbon liquid is degassed during the filling step.

40. The hyperthermic treatment of Claim 39, wherein the perfluorocarbon liquid is substantially degassed at least during the filling step.

41. The hyperthermic treatment of Claim 19, further comprising, during the heating step, irradiating the malignant cells with ionizing radiation.

42. The hyperthermic treatment of Claim 41, further comprising the step of oxygenating the liquid medium in the liquid-filled pulmonary air passages.

43. The hyperthermic treatment of Claim 42, wherein ultrasound in the frequency range of from about 2 MHz to about 3 MHz is transmitted through the pulmonary air passages filled with a perfluorocarbon liquid oxygenated to no more than about 75 percent saturation.

44. The hyperthermic treatment of Claim 42, wherein ultrasound in the frequency range of from about 250 KHz to about 1.5 MHz is transmitted through the pulmonary air passages filled with a perfluorocarbon liquid oxygenated to no more than about 50 percent saturation.

45. The hyperthermic treatment of Claim 19, wherein the liquid medium comprises a therapeutic agent.

46. The hyperthermic treatment of Claim 19, further comprising the step of introducing a chemotherapeutic agent into the liquid-filled pulmonary air passages.

47. The hyperthermic treatment of Claim 19, wherein the liquid medium is circulated during the heating step between the liquid-filled air passages and an exogenous reservoir.

48. A device for temporarily filling preselected pulmonary air passages with a heated liquid while maintaining gaseous ventilation of pulmonary air passages not filled with the liquid, the device comprising:

a first catheter having an axial bore for providing liquid communication between the proximal and distal ends of the device,

a first inflatable seal means having a lumen disposed concentrically around the first catheter at a fixed location near the distal end of the device,

a second catheter having an axial bore providing fluid communication between the proximal end of the device and the lumen of the first inflatable seal means, and

a third catheter having an axial bore providing gaseous communication between the proximal end of the device and a gas ventilation port disposed proximal to the first inflatable seal means.

49. The device of Claim 48, further comprising a second inflatable seal means disposed between the gas ventilation port and the first inflatable seal means.

50. The device of Claim 48, wherein the first catheter is thermally insulated from the proximal end of the device to the first inflatable seal means.

51. The device of Claim 48, further comprising temperature and pressure sensor means disposed distal to the first inflatable seal means.

52. The device of Claim 51, further comprising temperature and pressure sensor means disposed proximal to the inflatable seal means.

53. A device for temporarily filling preselected pulmonary air passages with a heated liquid while maintaining gaseous ventilation of pulmonary air passages not filled with the liquid, the device comprising:

a first catheter having an axial bore for providing gaseous communication between the proximal and distal ends of the device,

a first inflatable seal means having a lumen disposed concentrically around the first catheter at a fixed location near the distal end of the device,

a second catheter having an axial bore for providing fluid communication between the proximal end of the device and the lumen of the first inflatable seal means, and

a third catheter having an axial bore for providing liquid communication between the proximal end of the device and a port disposed proximal to the first inflatable seal means.

54. The device of Claim 53, further comprising a fourth catheter having an axial bore for providing liquid communication between the proximal end of the device and a port disposed proximal to the distal port of the third catheter.

55. The device of Claim 53, further comprising an ultrasonic transducer disposed proximal to the first inflatable seal means.

56. A device for temporarily occluding a preselected pulmonary air passage, comprising a catheter housing an axial bore for providing gaseous communication between the proximal end of the device and an inflatable seal means disposed at the distal end of the device.

57. A device for providing ultrasonic heating at a preselected pulmonary air passage, the device comprising:

a first catheter having an axial bore for providing gaseous communication between the proximal and distal ends of the device,

an inflatable seal means having a lumen disposed concentrically around the first catheter at a fixed location near the distal end of the delivery device,

a transducer assembly comprising a distensible sac disposed proximal to the inflatable seal means and an ultrasonic transducer disposed within the distensible sac, and

a second catheter having an axial bore for providing liquid communication between the proximal end of the device and the distensible sac.

58. The device of Claim 57, further comprising a third catheter having an axial bore for providing fluid communication between the proximal end of the device and a port disposed proximal to the inflatable seal means.

59. The device of Claim 58, further comprising an additional catheter having an axial bore for providing in cooperation with the second catheter circulating liquid communication between the proximal end of the device and the distensible sac.

60. The device of Claim 58, further comprising means for providing optical communication between the proximal and distal ends of the device.

61. The device of Claim 58, wherein said transducer assembly includes one or more ultrasound transducers coaxially arranged around said first conduit and a manifold for distributing liquid around said transducer.

62. A device for providing ultrasonic heating to an internal body cavity, the device comprising a transducer assembly comprising a distensible sac and an ultrasound transducer disposed within the distensible sac, and at least one conduit for providing fluid communication between the proximal end of the device and the distensible sac.

AMENDED CLAIMS
[received by the International Bureau
on 28 December 1990 (28.12.90);
new claims 63-82 added; other claims unchanged (4 pages)]

59. The device of Claim 58, further comprising an additional catheter having an axial bore for providing in cooperation with the second catheter circulating liquid communication between the proximal end of the device and the distensible sac.

60. The device of Claim 58, further comprising means for providing optical communication between the proximal and distal ends of the device.

61. The device of Claim 58, wherein said transducer assembly includes one or more ultrasound transducers coaxially arranged around said first conduit and a manifold for distributing liquid around said transducer.

62. A device for providing ultrasonic heating to an internal body cavity, the device comprising a transducer assembly comprising a distensible sac and an ultrasound transducer disposed within the distensible sac, and at least one conduit for providing fluid communication between the proximal end of the device and the distensible sac.

63. A process for controlling, diagnosing or treating physiological conditions, diseases or abnormalities of a patient, said process comprises passing a liquid medium through at least a portion of said patient's pulmonary air passages by liquid lavage ventilation, said liquid medium comprises at least one biological agent and a liquid carrier.

64. A process as recited in Claim 63 wherein said pulmonary air passages comprise said patient's endotracheal tube, pulmonary canals, spaces or volumes in the trachea, left and right bronchi, bronchiolus, and/or alveoli of the lungs and the like.

65. A process as recited in Claim 63 wherein at least one of said physiological conditions, diseases or abnormalities controlled, diagnosed or treated is pulmonary-related cancer.

66. A process as recited in Claim 65 wherein at least one of said physiological diseases or abnormalities controlled, diagnosed or treated is bronchial carcinoma.

67. A process as recited in Claim 65 wherein said biological agent comprises at least one anti-cancer agent.

68. A process as recited in Claim 67 wherein said anti-cancer agent comprises an agent selected from the group consisting of adriamycin, toxins, antibody-linked radionuclides and combinations thereof.

69. A process as recited in Claim 63 wherein said liquid carrier is at least partially breathable.

70. A process as recited in Claim 69 wherein said breathable liquid carrier comprises perfluorocarbon.

71. A process as recited in Claim 70 wherein said process is a hyperthermic treatment of lung cancer and wherein said perfluorocarbon is characterized by an average molecule weight in the range from about 350 to about 560.

72. A process as recited in Claim 71 wherein said perfluorocarbon is characterized by having:

a. viscosity less than about 5 CP at 25°C,

b. density less than about 2.0 g/cm^3 at 25°C,

c. boiling point greater than about 55°C,

d. vapor pressure in the range of from about 20 TORR to about 200 TORR, and

e. Prandtl number less than about 10 at 25°C.

73. A process as recited in Claim 70 wherein said perfluorocarbon is selected from the group consisting of FC-84, FC-72, RM-82, FC-75 RM-101, dimethyladamantane, trimethylbicyclononane, and perfluorodecalin.

74. A process as recited in Claim 63 wherein, before or during said control, diagnosis or treatment, said liquid carrier temperature ranges from between about said patient's normal body temperature to about 20% above said patient's normal body temperature.

75. A process as recited in Claim 63 wherein, before or during said control, diagnosis or treatment, said liquid carrier temperature ranges from between about said patient's normal body temperature to about 20% below said patient's normal body temperature.

76. A process as recited in Claim 75 wherein said physiological conditions, diseases or abnormalities controlled, diagnosed or treated is pulmonary-related cancer and wherein said process comprises the steps of:

a. temporarily filling preselected pulmonary air passages adjoining pulmonary tissues comprising malignant cells with a liquid medium, said liquid medium comprising at least one biological agent and a liquid carrier,

b. heating the adjoining pulmonary tissues comprising the malignant cells to a temperature in the range of from about 40°C to about 50°C for a period of time by transmitting ultrasound through the liquid-filled pulmonary air passages, and

c. thereafter removing the liquid medium from the patient's pulmonary air passages.

77. A process as recited in Claim 76 wherein said liquid carrier is at least partially breathable.

78. A process as recited in Claim 77 wherein said breathable liquid carrier comprises at least one liquid selected from the group consisting of perfluorochemicals, saline, silicone, and vegetable oils and combinations thereof.

79. A process as recited in Claim 78 wherein said breathable liquid comprises perfluorocarbon liquid.

80. A process as recited in Claim 79 wherein said perfluorocarbon liquid is characterized by having:

a. viscosity less than about 5 CP at 25°C,

b. density at less than about 2.0 g/cm^3 at 25°C,

c. boiling point greater than about 75°C,

d. vapor pressure in the range of from about 25 TORR to about 100 TORR;

e. acoustic impedance in the range of from about 8.0 to about 1.6 Mega Rayls at 37°C,

f. acoustic attenuation less than about 1.2 dB/cm at 1.0 MHz and 45°C, and

g. an acoustic intensity of about 3 W/cm^2.

81. A process as recited in Claim 78 wherein said breathable comprises physiological saline.

82. A process as recited in Claim 76 wherein said ultrasound is in the frequency range of from about 250 KHz to about 3 MHz.

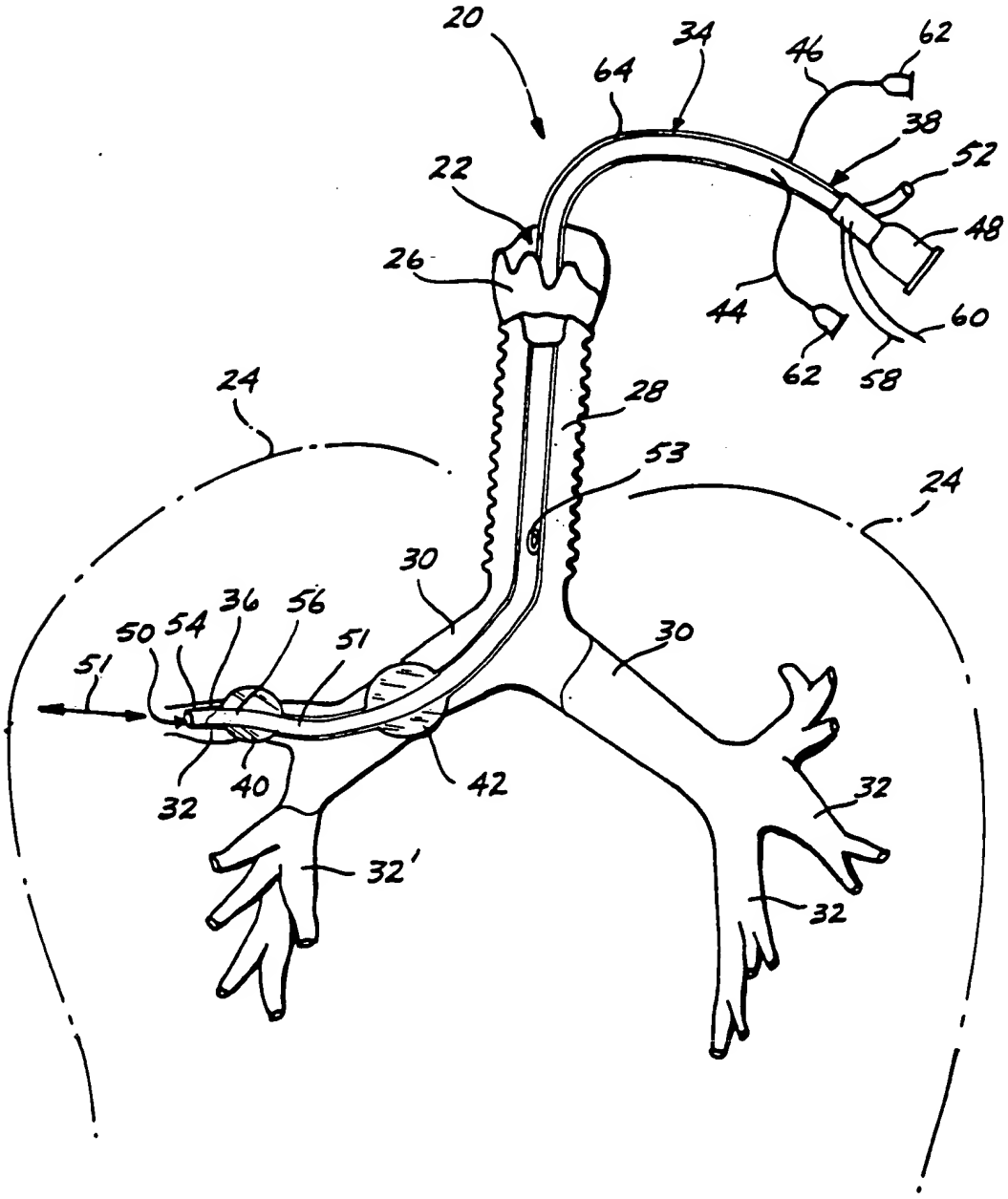

20
34
64
46
62
38
52
22
48
26
44
60
62
58
24
28
53
24
30
36
56
50
54
51
51
30
32
40
42
32
32'
32

Fig. 1.

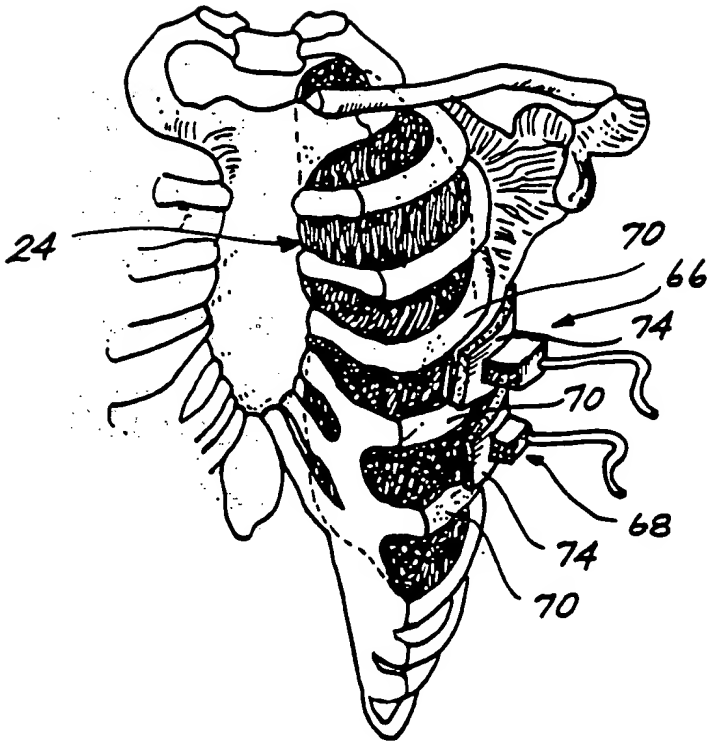


Fig. 2.

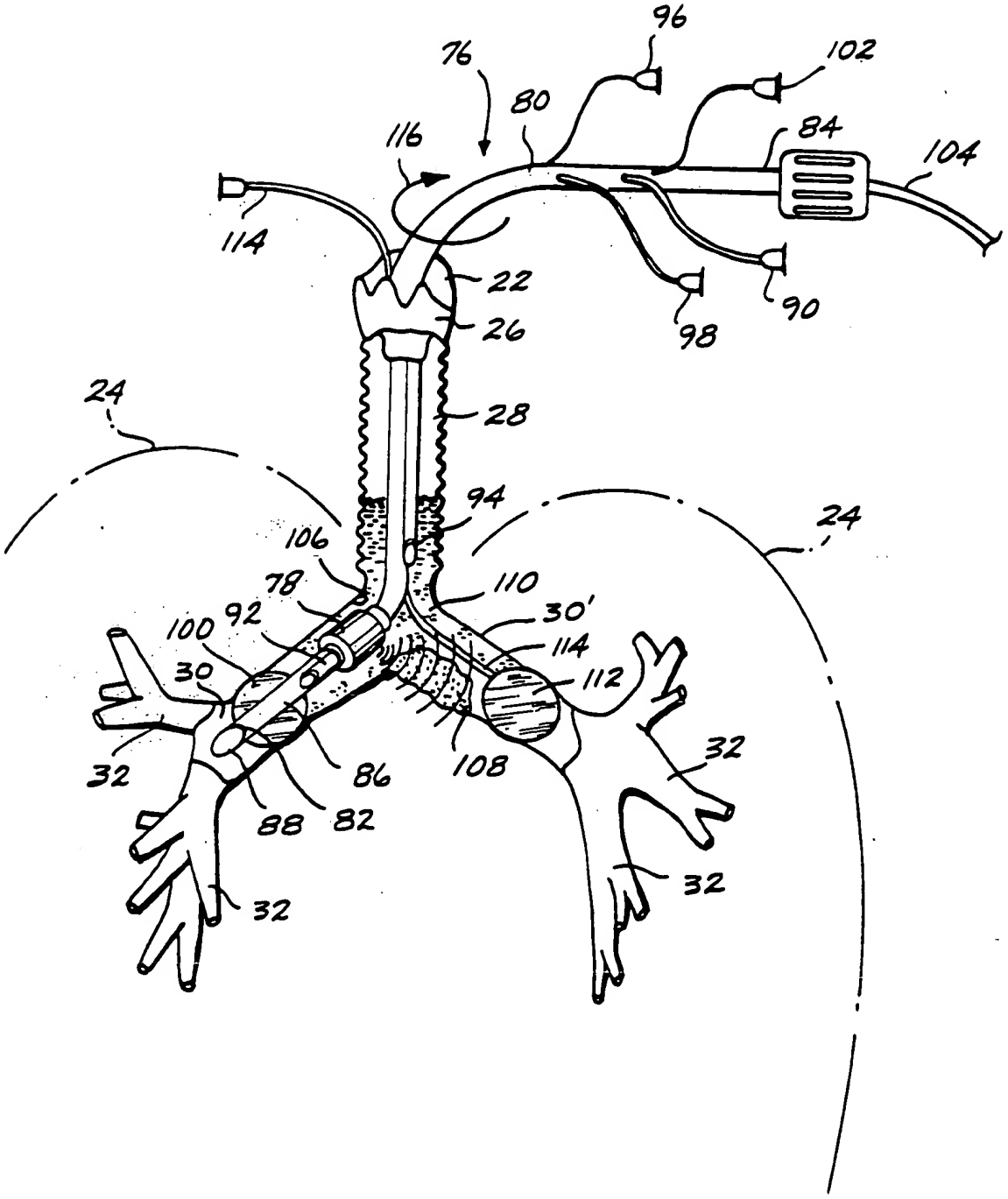

96
102
76
80
84
104
116
114
22
26
90
98
24
28
94
24
106
78
110
30'
100
92
114
30
112
32
32
86
108
88
82
32
32

Fig. 3.

Fig. 4.

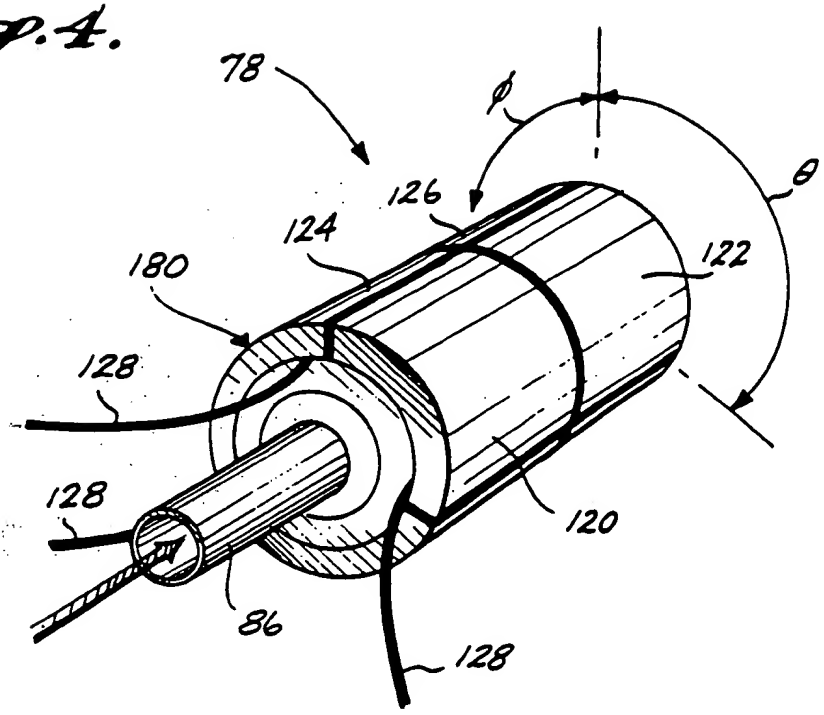
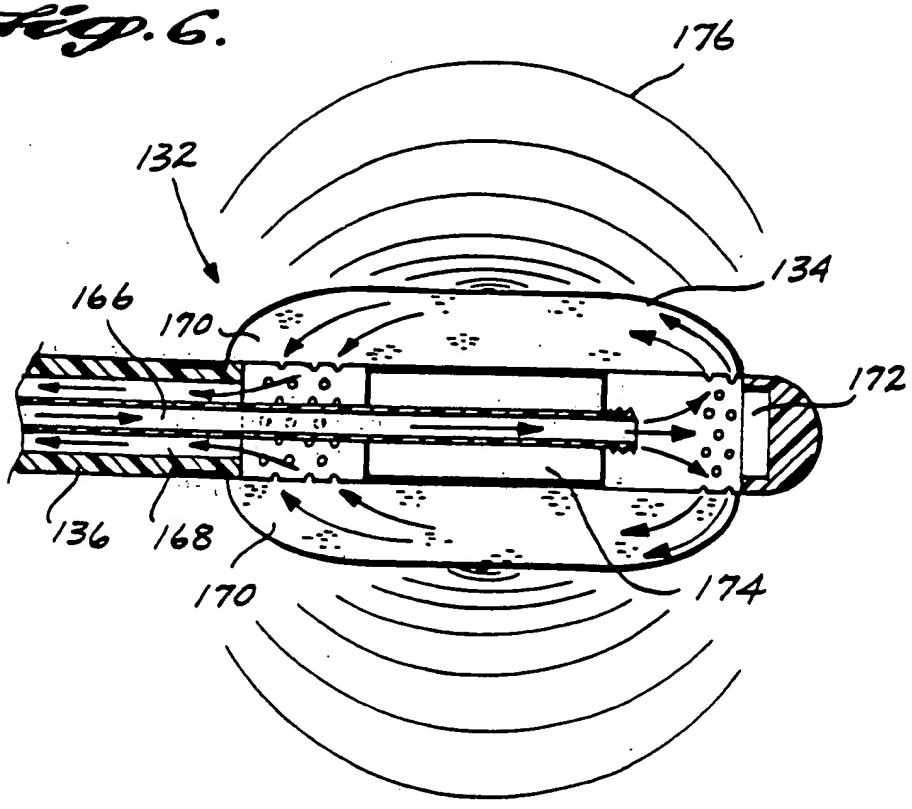

78
φ
θ
126
124
122
180
128
128
120
86
128

Fig. 6.


176
132
134
166
170
172
136
168
170
174

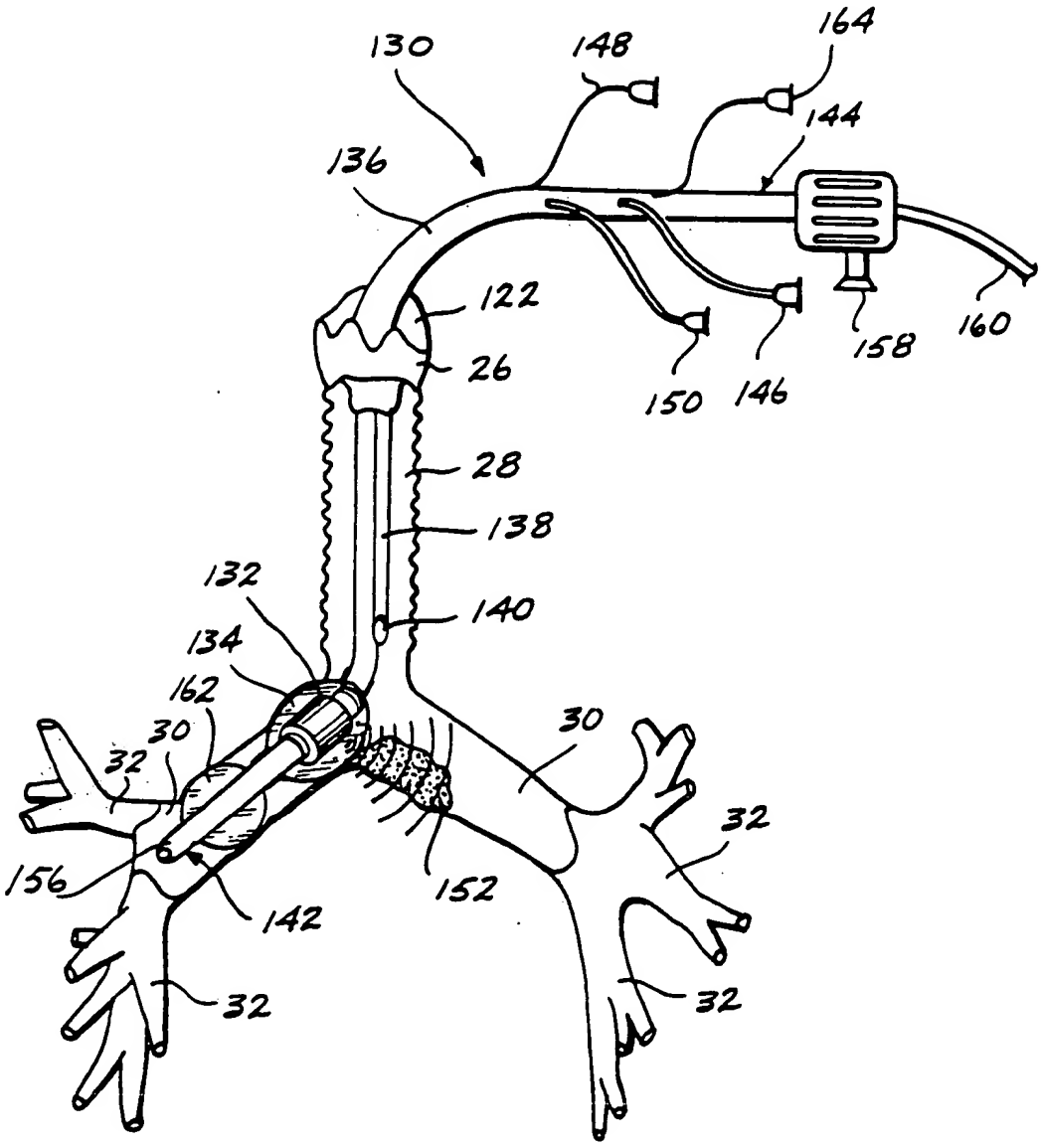

130
148
164
144
136
122
26
28
138
140
132
134
162
30
32
156
142
152
158
160
150
146

Fig. 5.

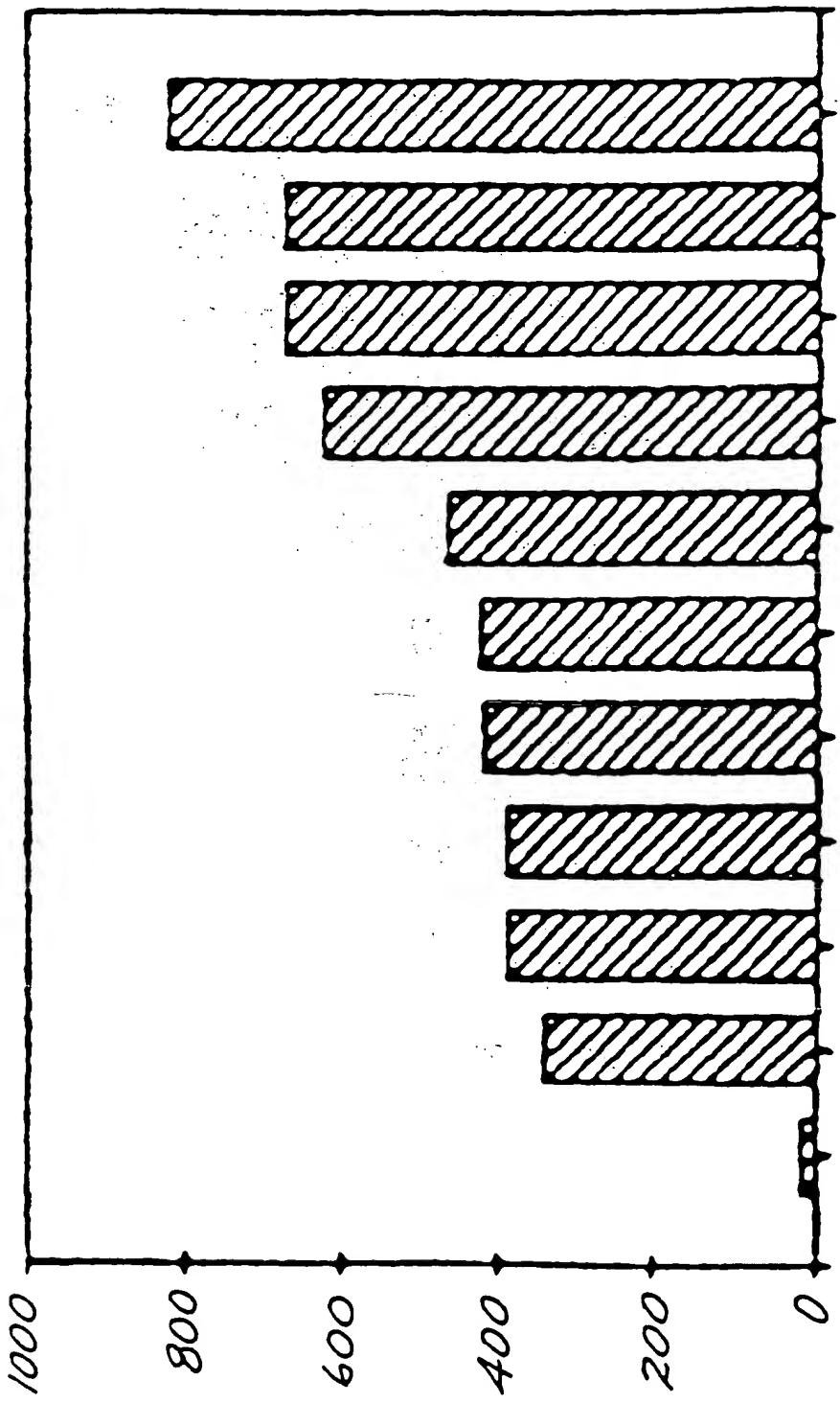

1000
800
600
400
200
0
H2O
FC-72
RM-82
FC-84
RM-101
F-DECALIN
FC-75
FC-43
FC-5311
RM-175
FC-5312

Fig. 7.

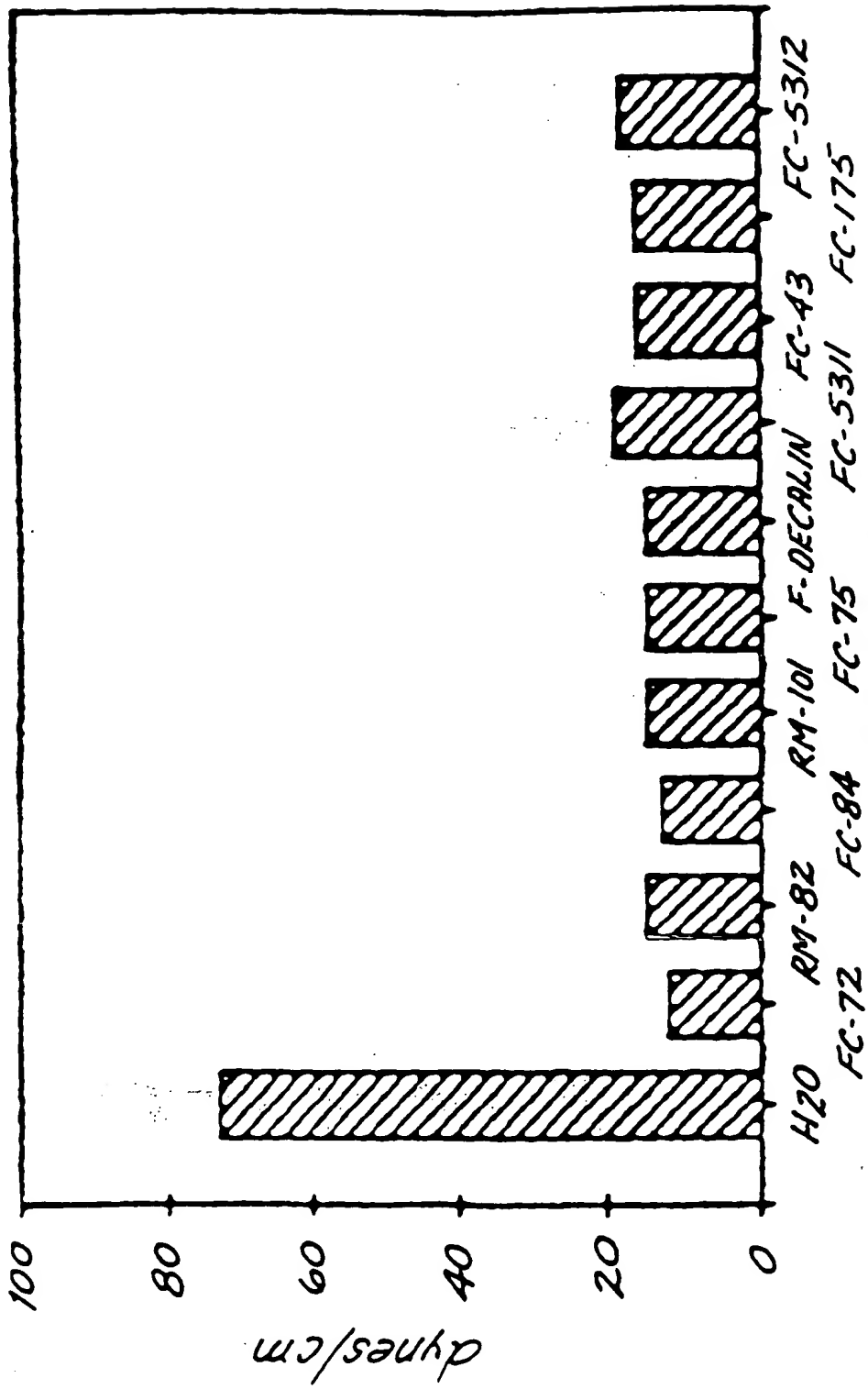

dynes/cm
100
80
60
40
20
0
H20
FC-72
RM-82
FC-84
RM-101
FC-75
F-DECALIN
FC-5311
FC-43
FC-175
FC-5312

Fig. 8.

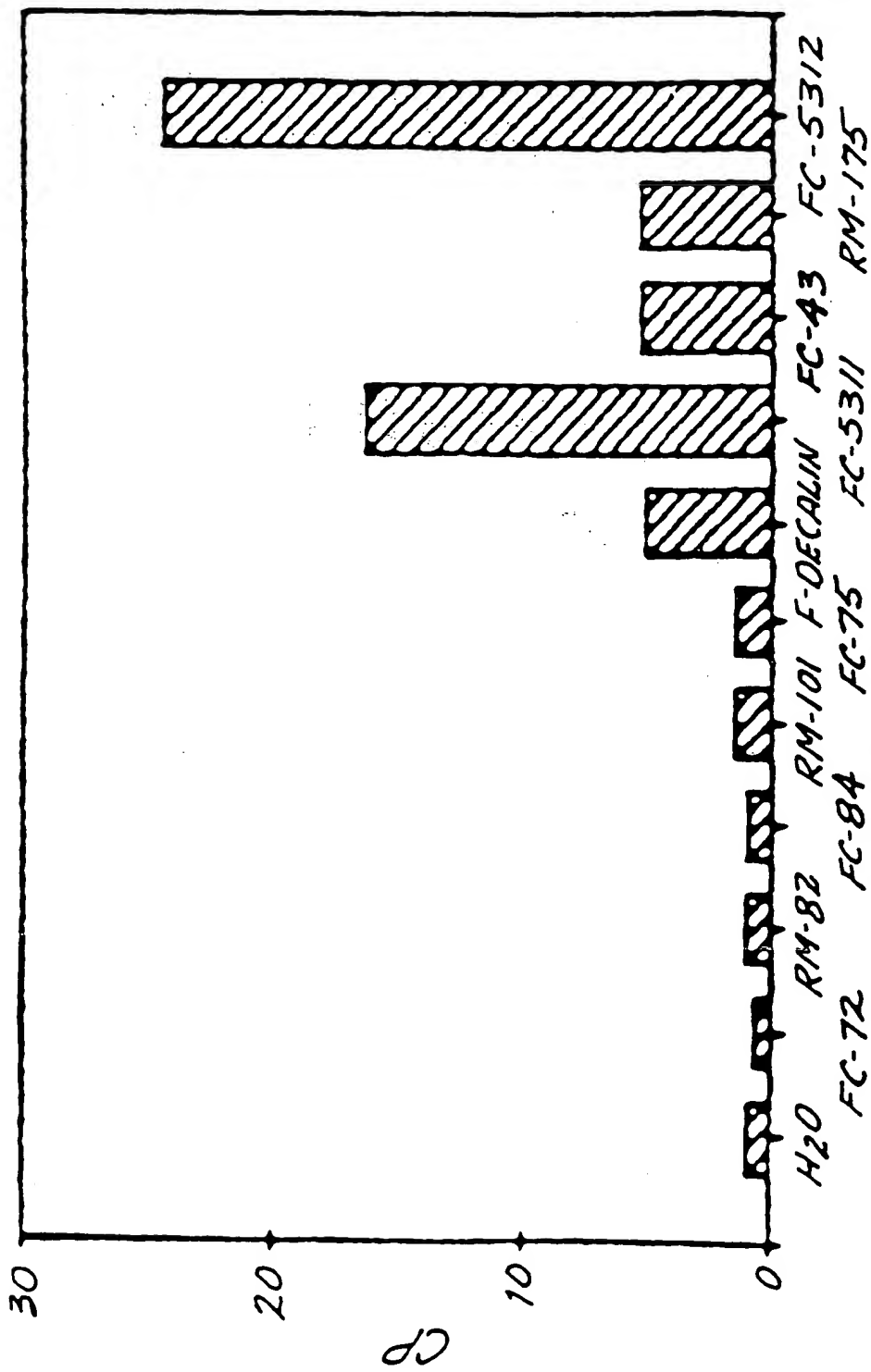

30
20
10
0
CP
H2O
FC-72
RM-82
FC-84
RM-101
FC-75
F-DECALIN
FC-5311
FC-43
RM-175
FC-5312

Fig. 9.

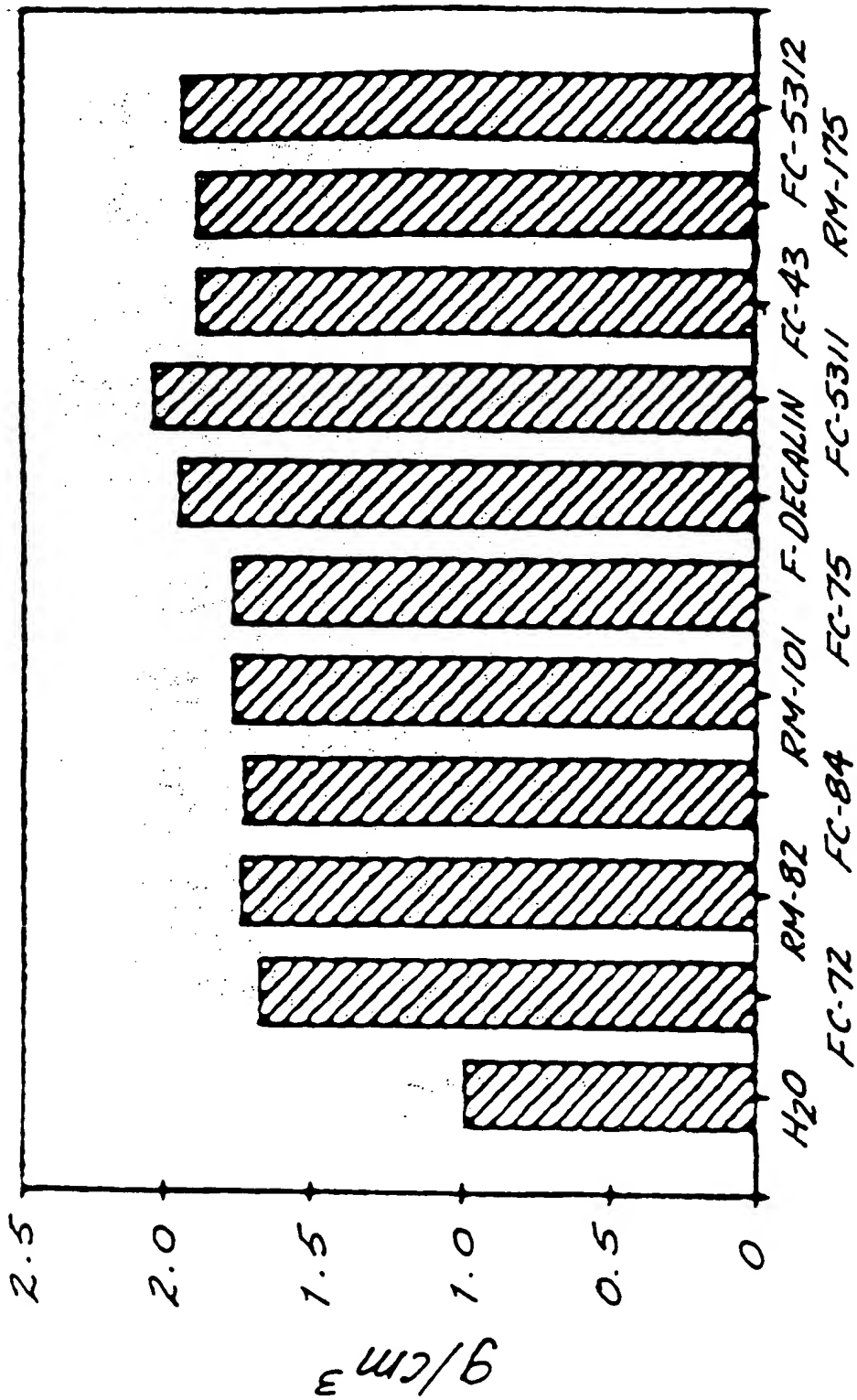

H2O
FC-72
RM-82
FC-84
RM-101
FC-75
F-DECALIN
FC-5311
FC-43
RM-175
FC-5312
2.5
2.0
1.5
1.0
0.5
0
g/cm3

Fig. 10.

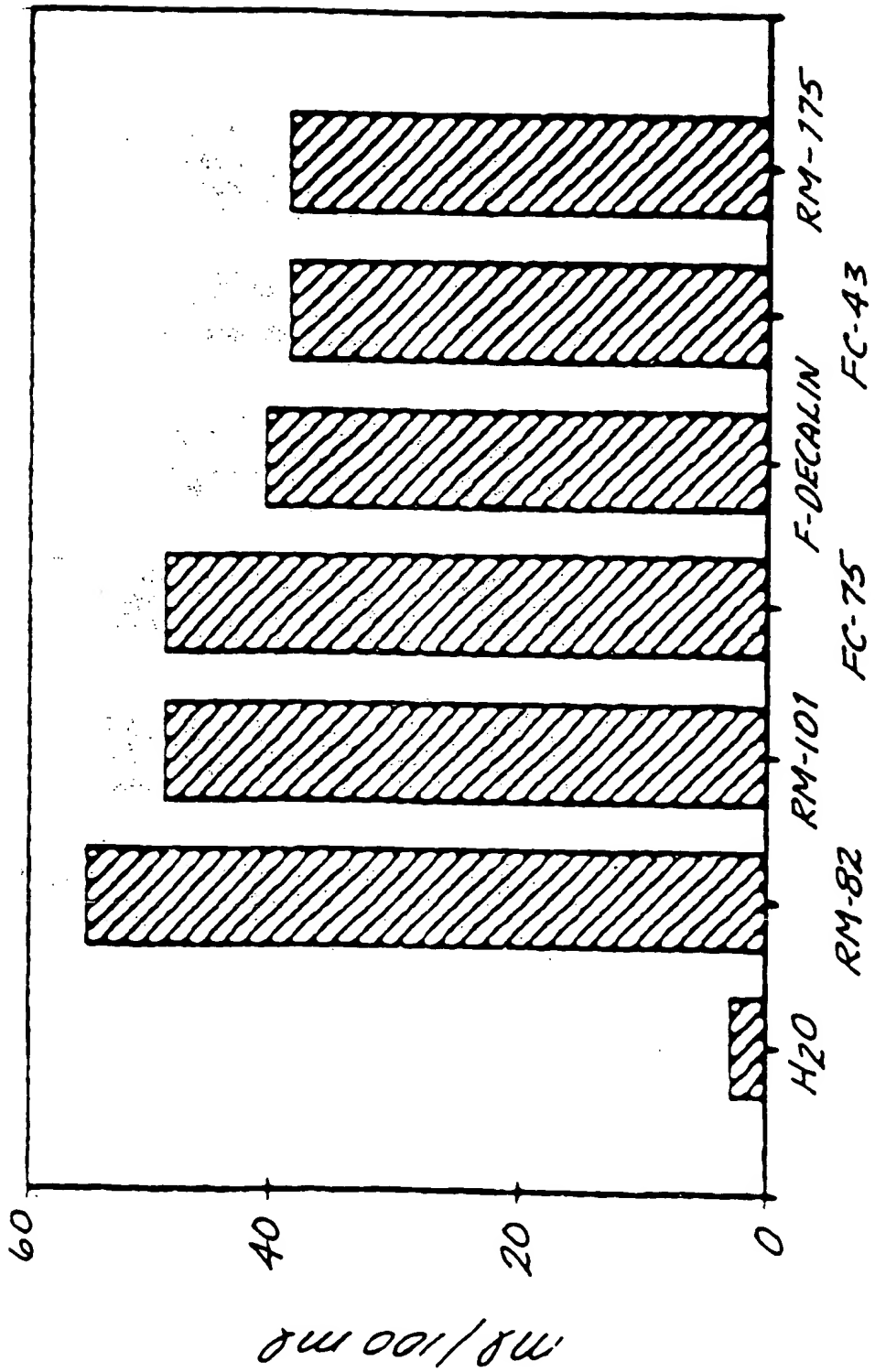


Fig. 11.

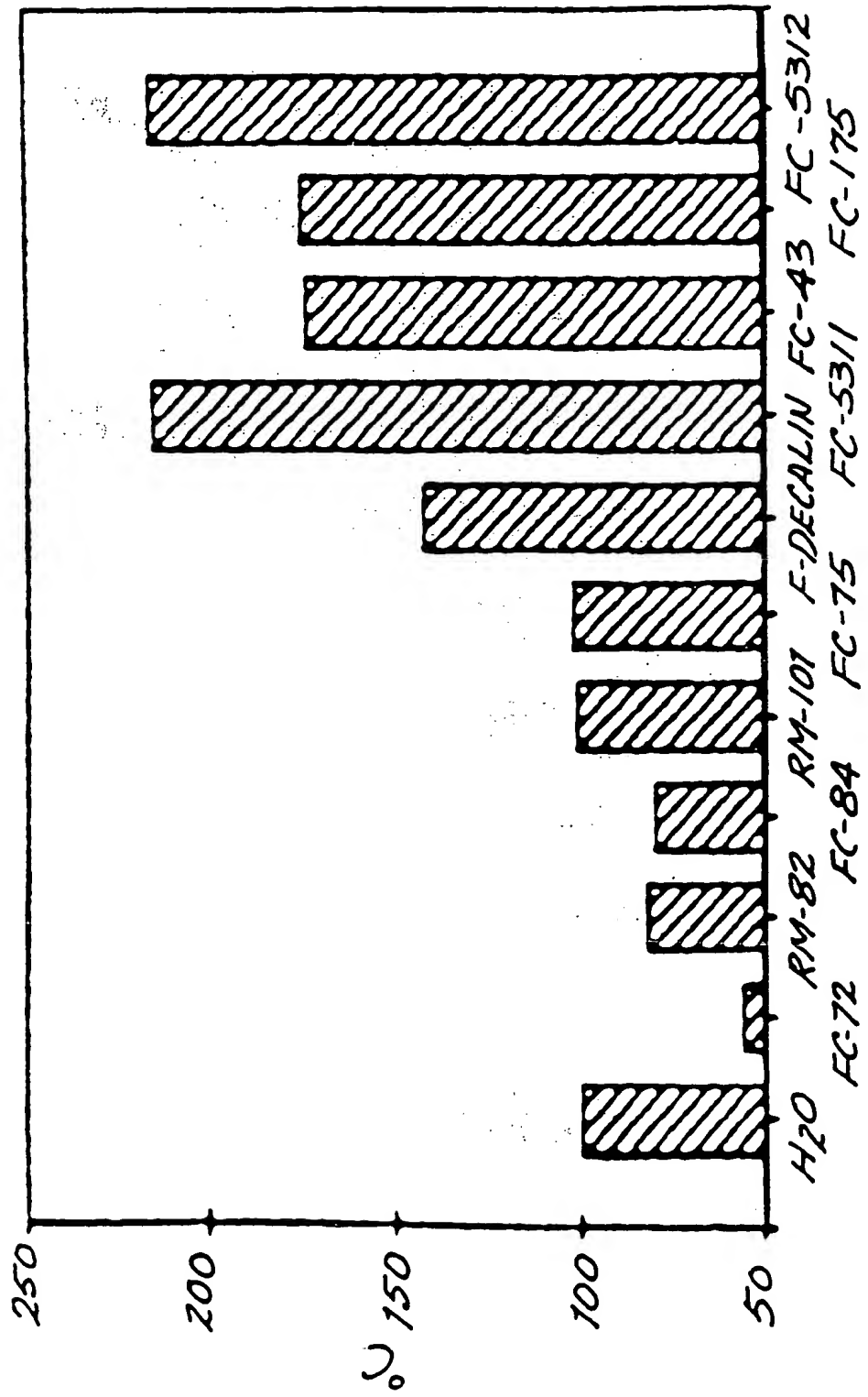

250
200
150
100
50
η_0
H_2O
FC-72
RM-82
FC-84
RM-101
FC-75
F-DECALIN
FC-43
FC-5311
FC-5312
FC-175

Fig. 12.

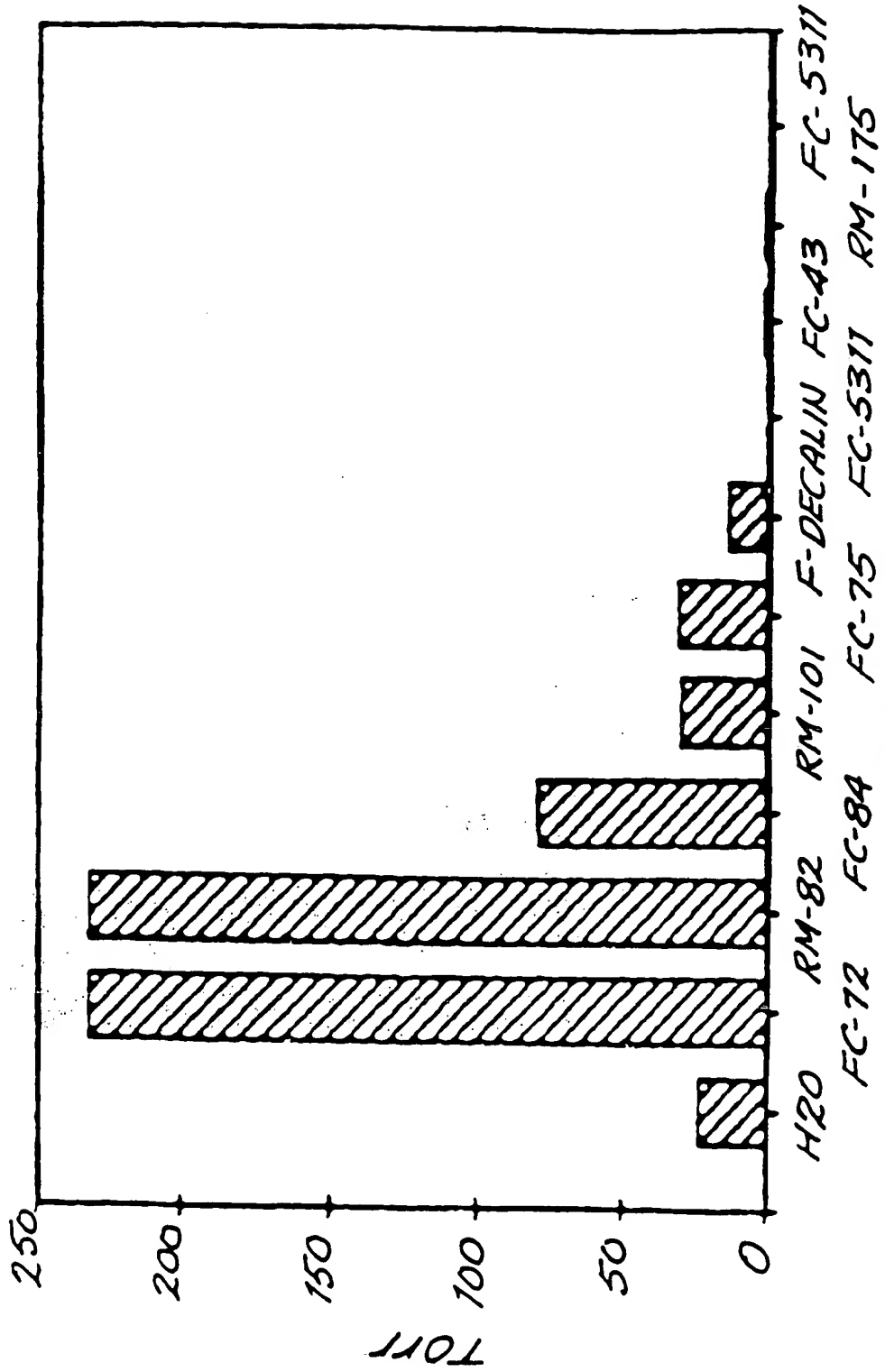
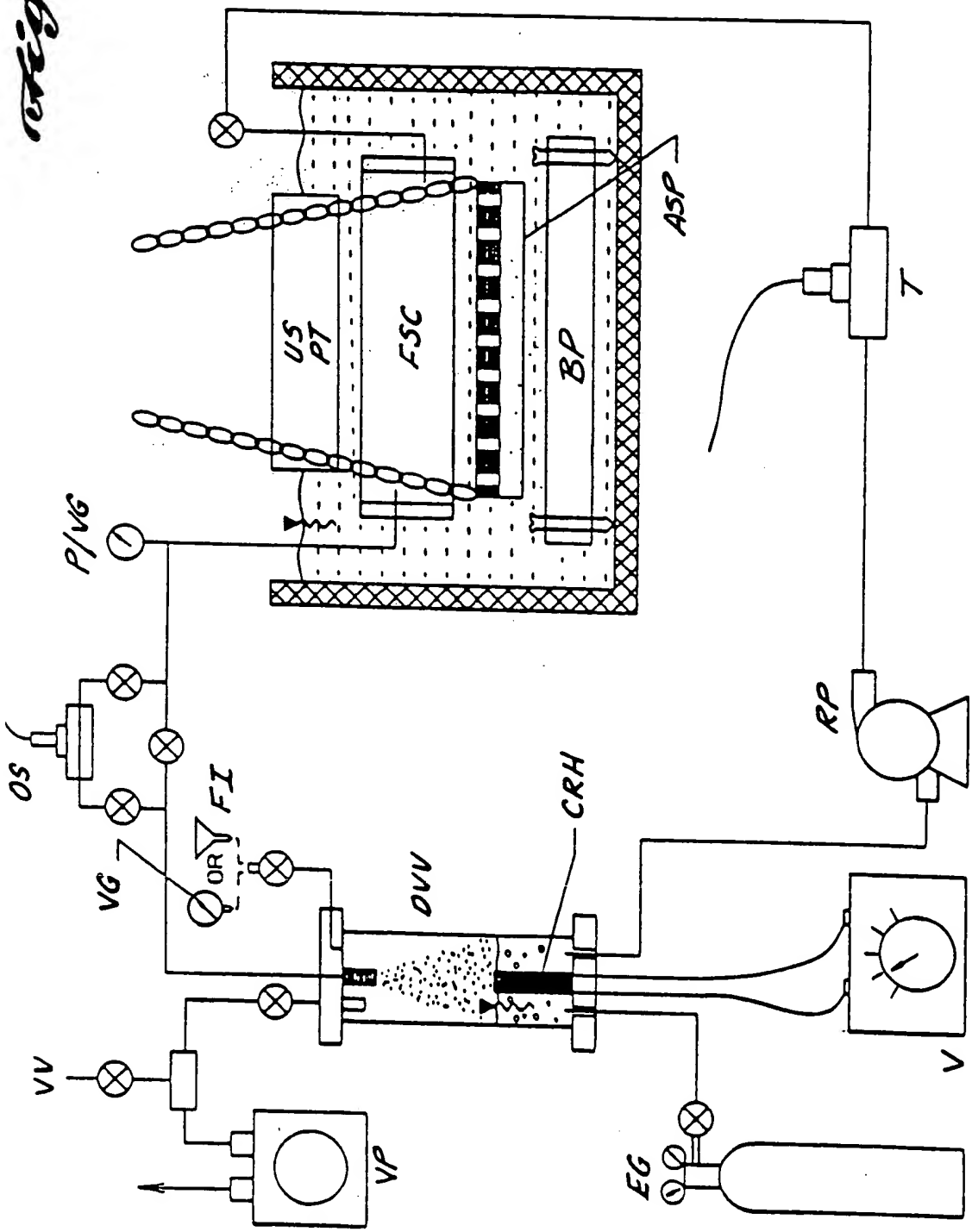

TORR
250
200
150
100
50
0
H20
FC-72
RM-82
FC-84
RM-101
FC-75
F-DECALIN
FC-5311
FC-43
RM-175
FC-5311

Fig. 13.

Fig. 1A.



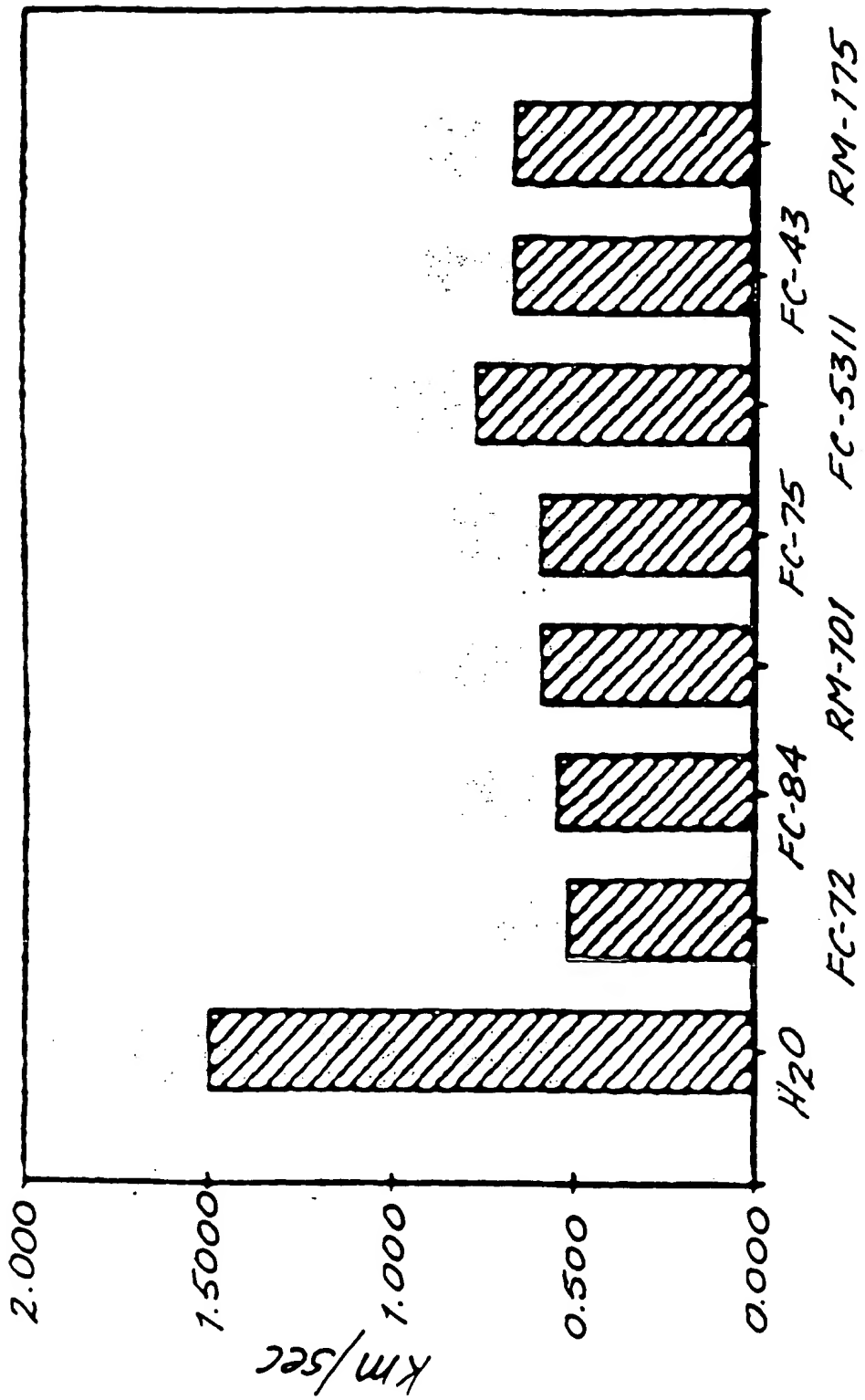

H20
FC-72
FC-84
RM-101
FC-75
FC-5311
FC-43
RM-175
0.000
0.500
1.000
1.5000
2.000
Km/sec

Fig. 15.

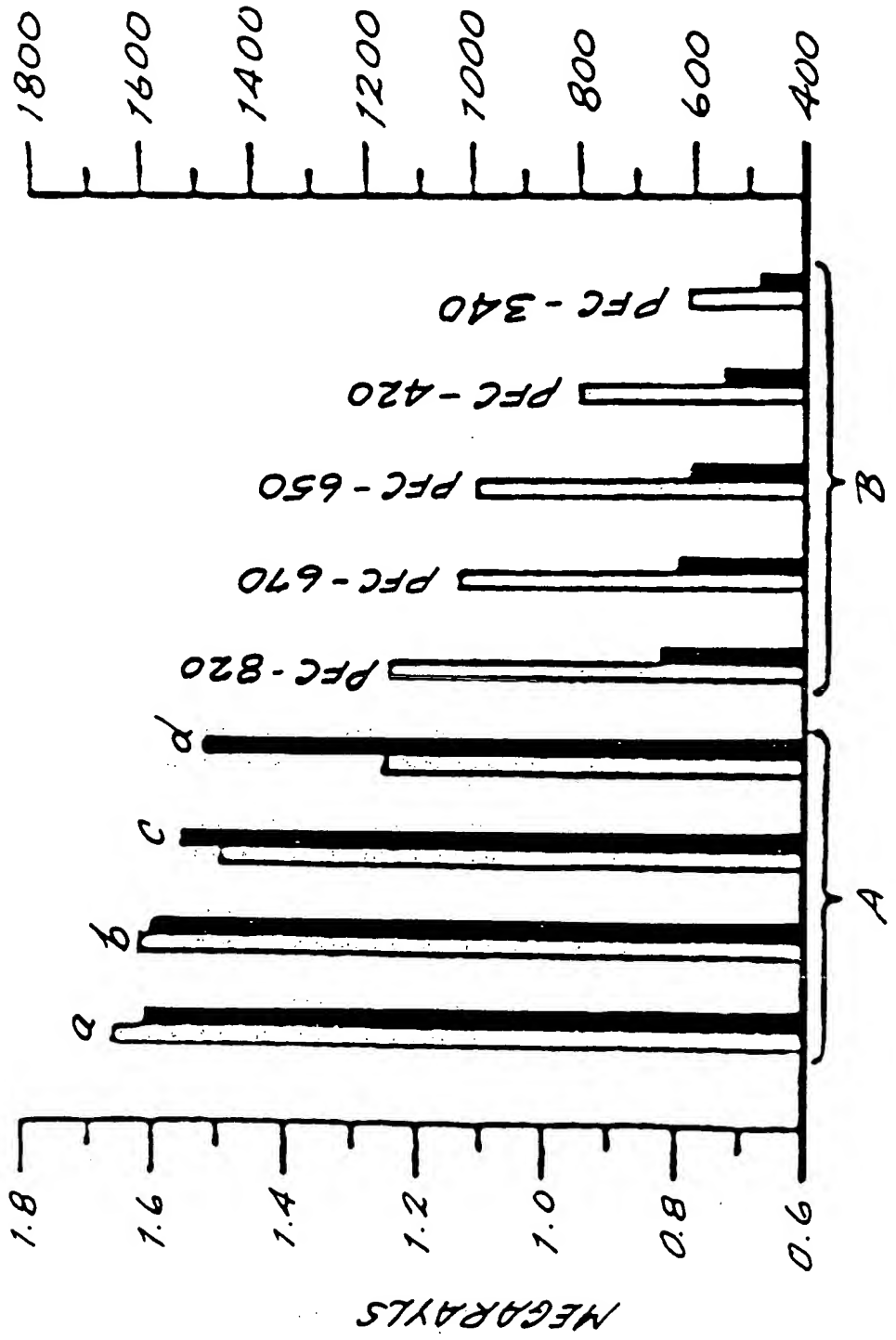

1800
1600
1400
1200
1000
800
600
400
PFC - 340
PFC - 420
PFC - 650
PFC - 670
PFC - 820
B
A
a
b
c
d
1.8
1.6
1.4
1.2
1.0
0.8
0.6
MEGARAYLS

Fig. 16.

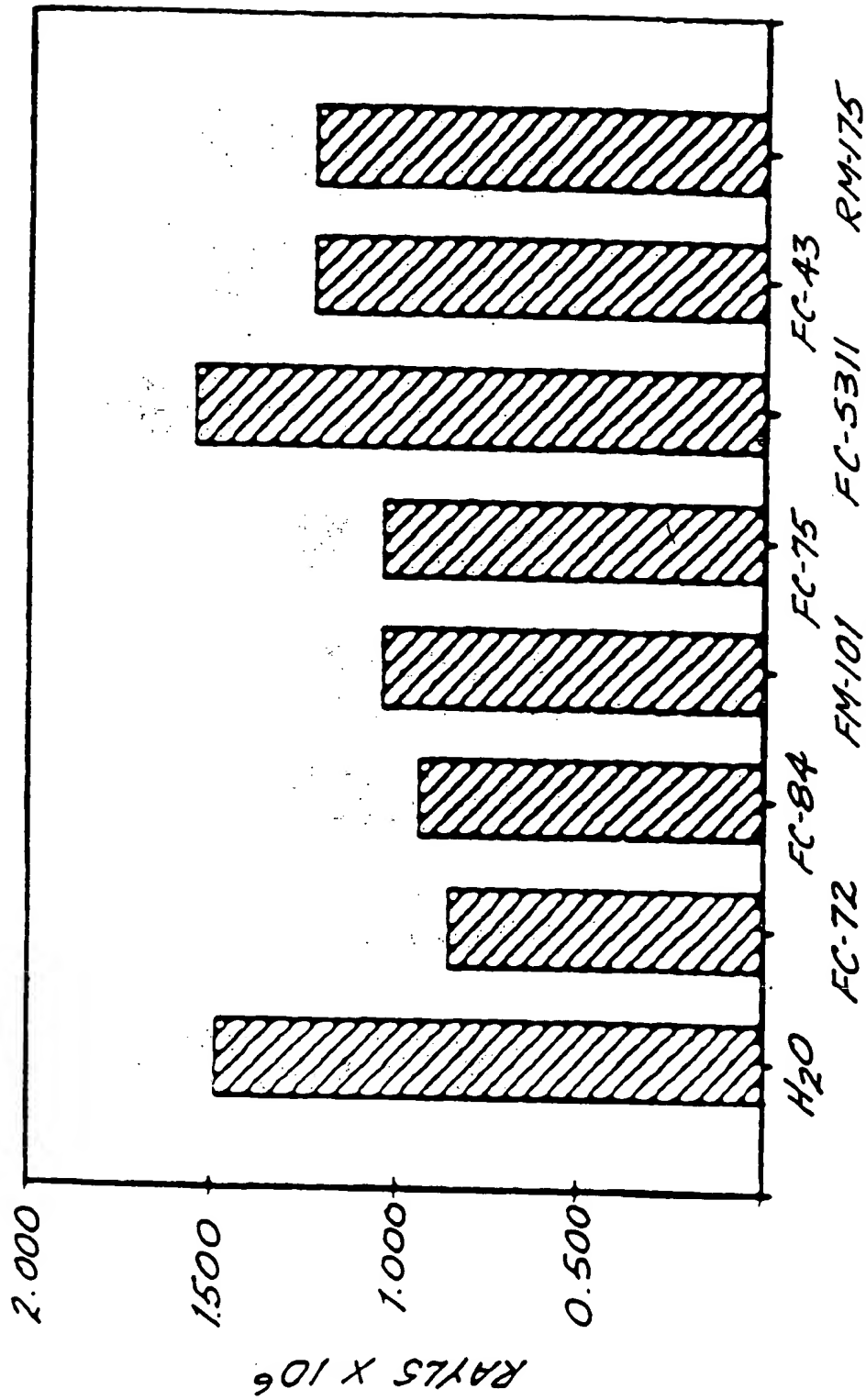

RM-175
FC-43
FC-5311
FC-75
FM-101
FC-84
FC-72
H2O
2.000
1.500
1.000
0.500
RATES X 10⁶

Fig. 17.

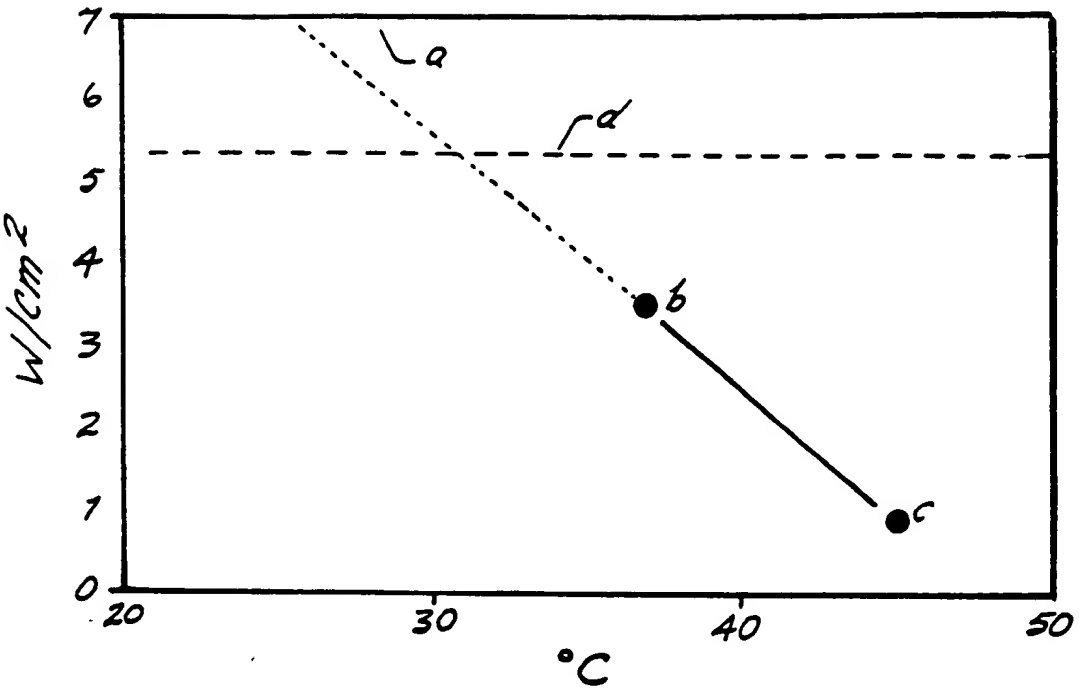


Fig. 18.

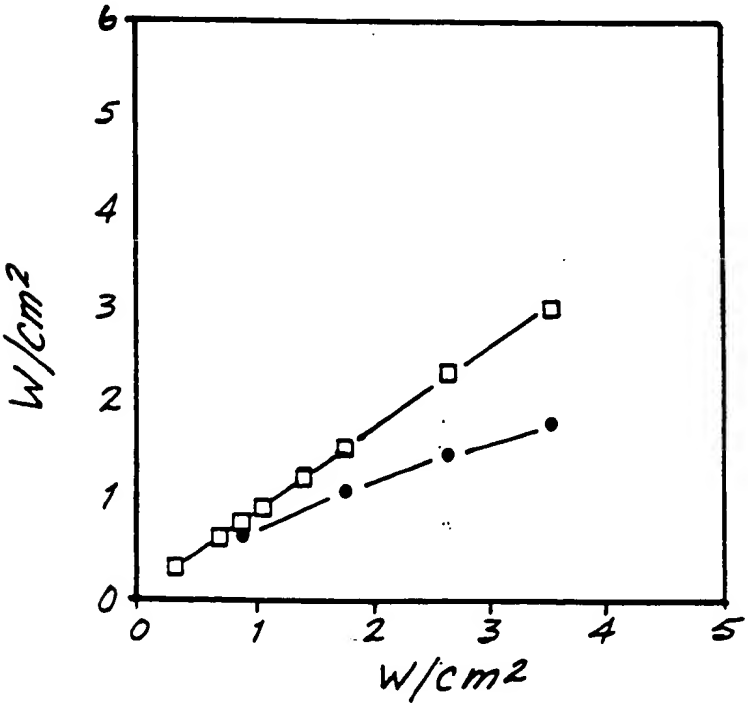


Fig. 19.

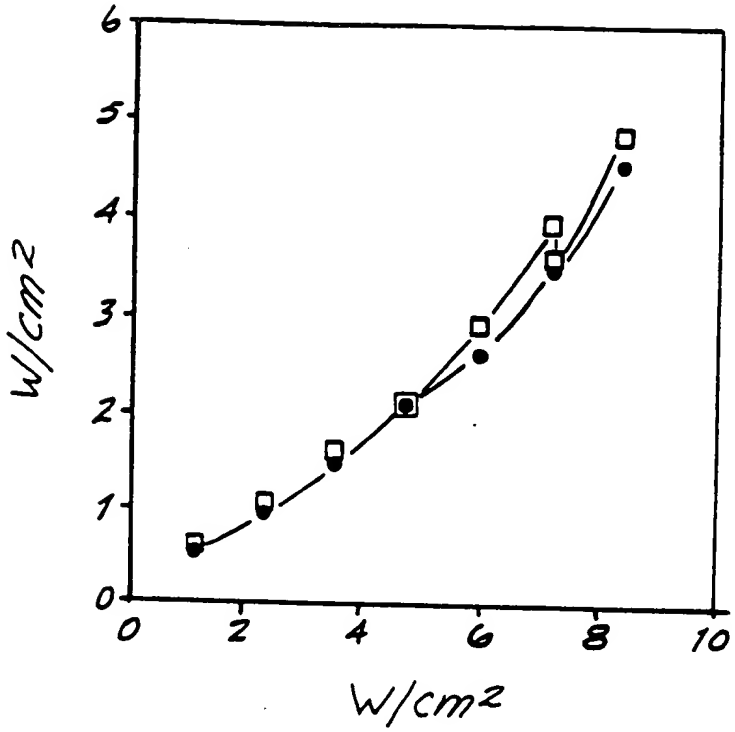


Fig. 20.

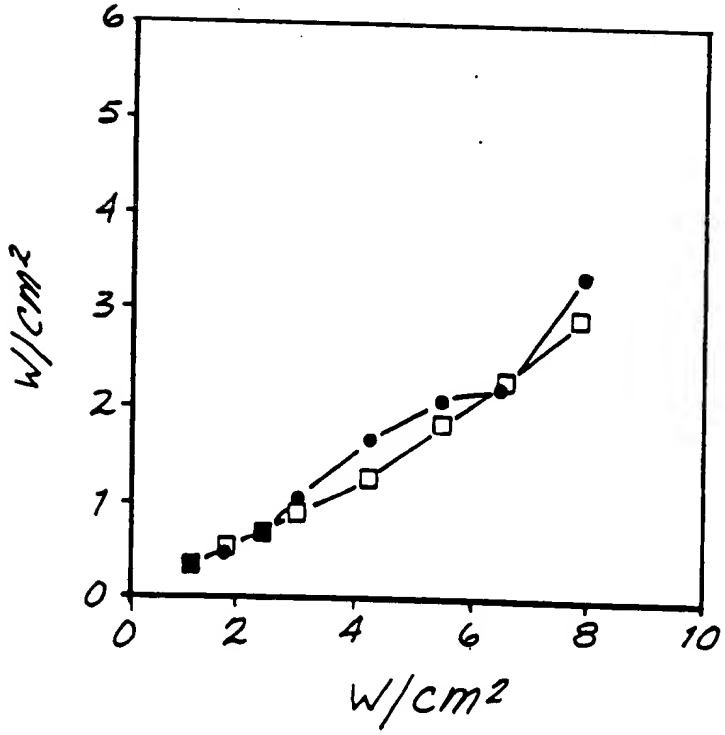


Fig. 21.

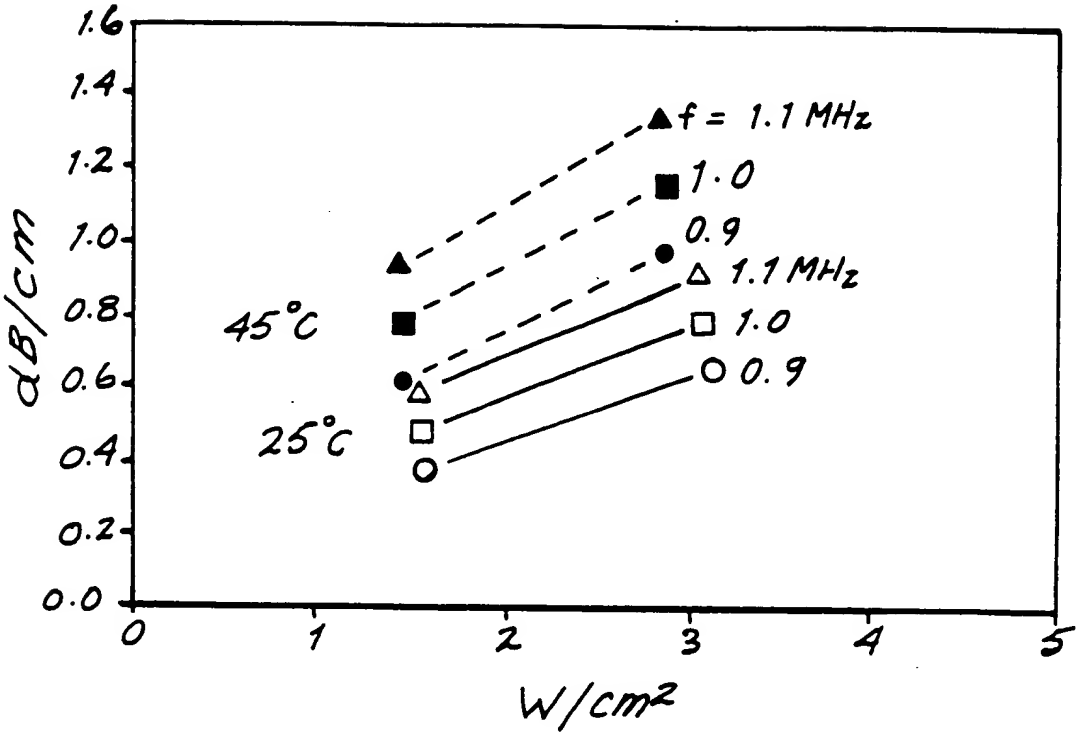


Fig. 22.

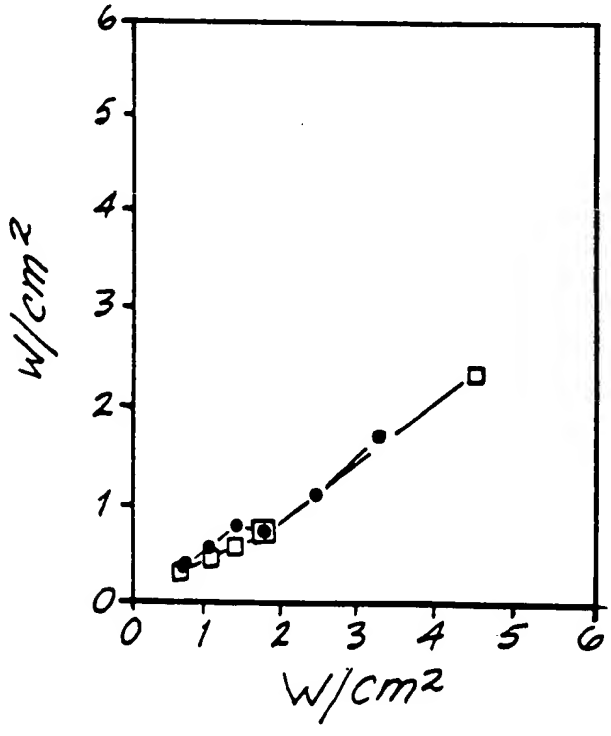


Fig. 23.

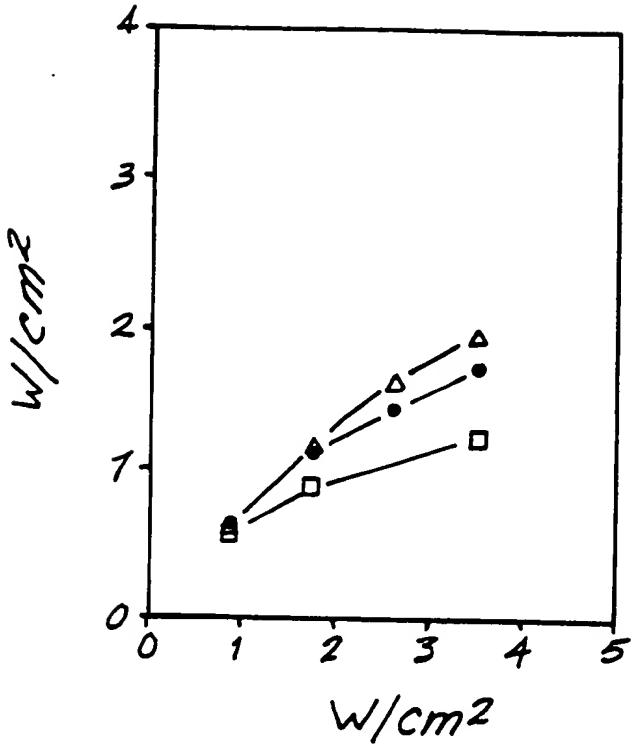

4
3
2
1
0
W/cm2
0
1
2
3
4
5
W/cm2

Fig. 24.

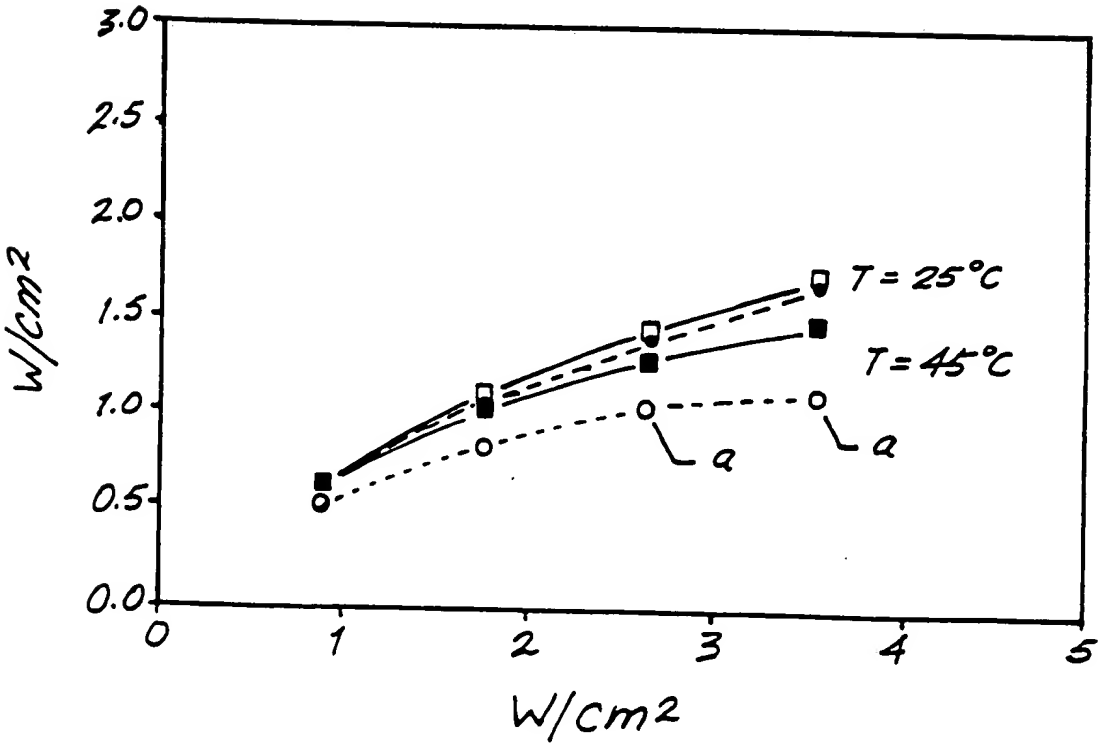

3.0
2.5
2.0
1.5
1.0
0.5
0.0
W/cm2
T = 25°C
T = 45°C
a
a
0
1
2
3
4
5
W/cm2

Fig. 25.

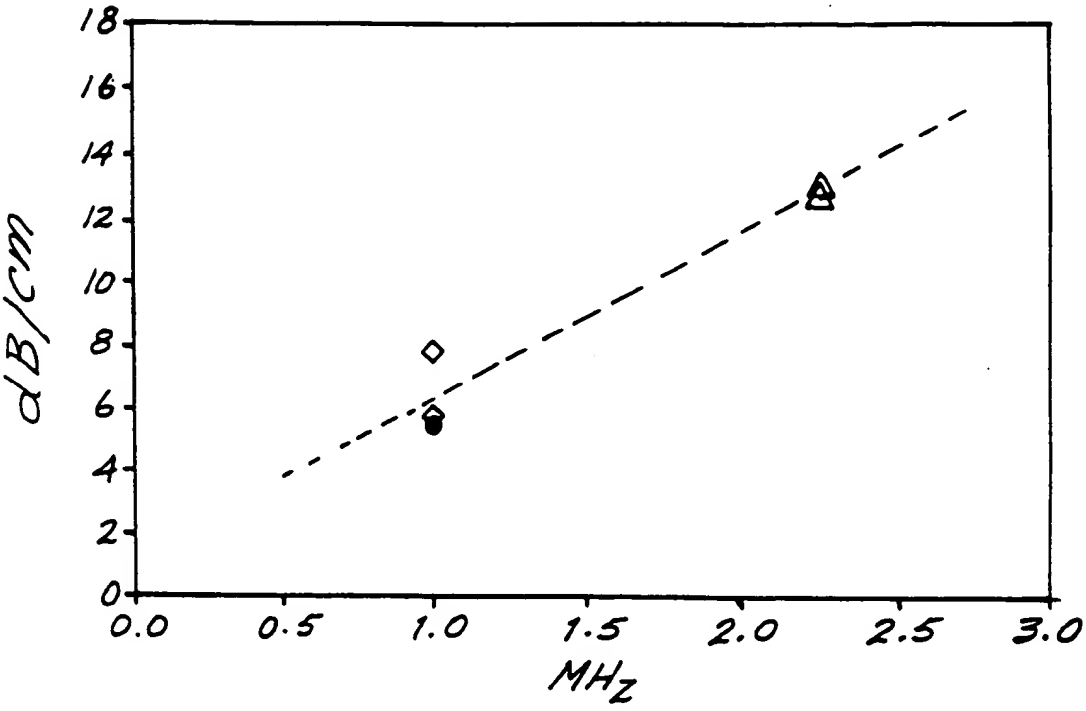

18
16
14
12
10
8
6
4
2
0
dB/cm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
MHz

Fig. 26.

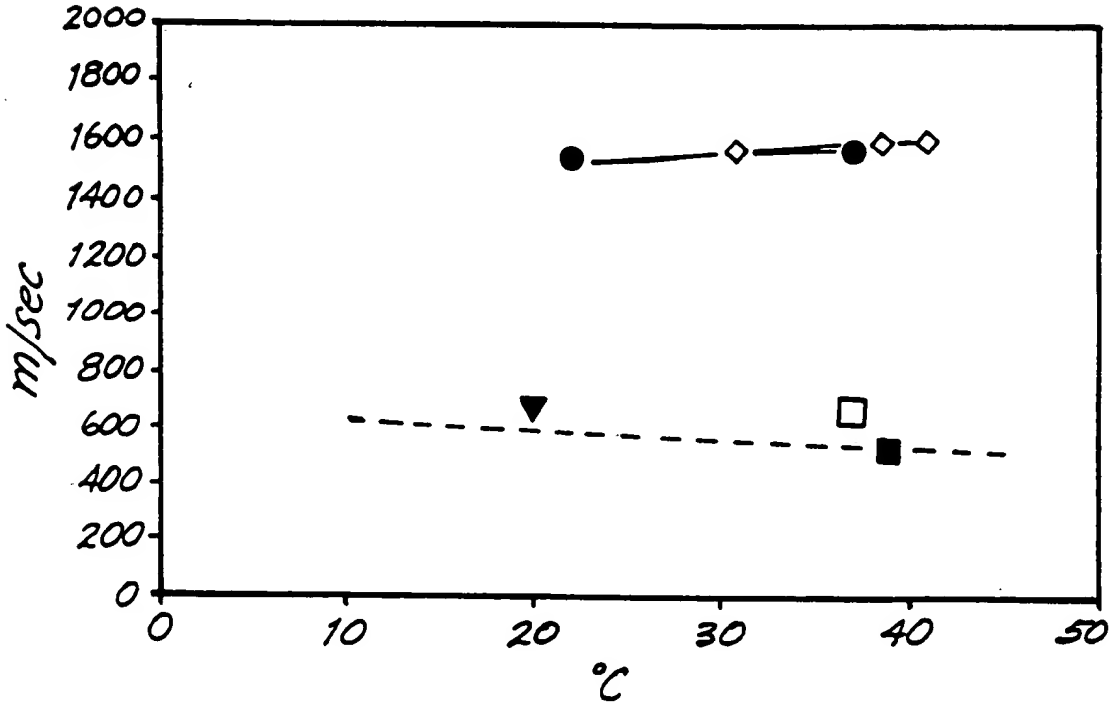

2000
1800
1600
1400
1200
1000
800
600
400
200
0
m/sec
0
10
20
30
40
50
°C

Fig. 27.

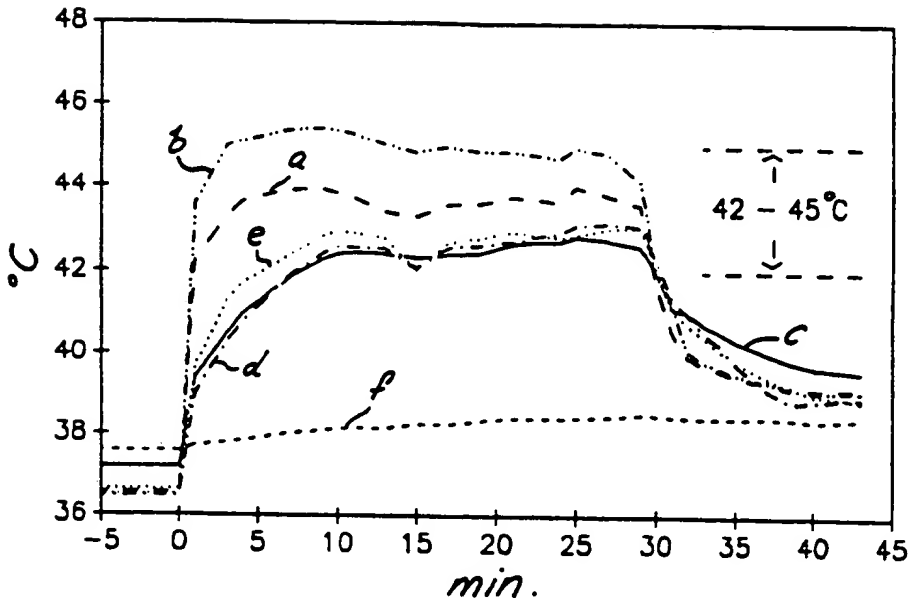

48
46
44
42
40
38
36
°C
-5
0
5
10
15
20
25
30
35
40
45
min.
42 – 45°C
a
b
c
d
e
f

Fig. 28.

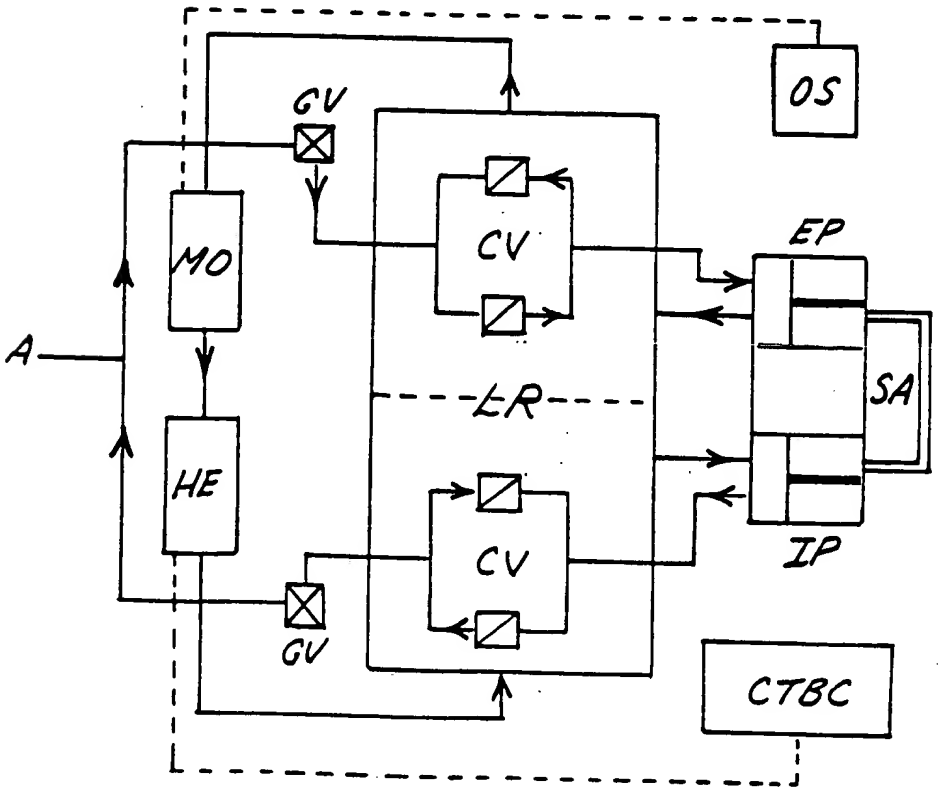

OS
GV
CV
EP
MO
A
SA
LR
HE
CV
IP
GV
CTBC

Fig. 29.

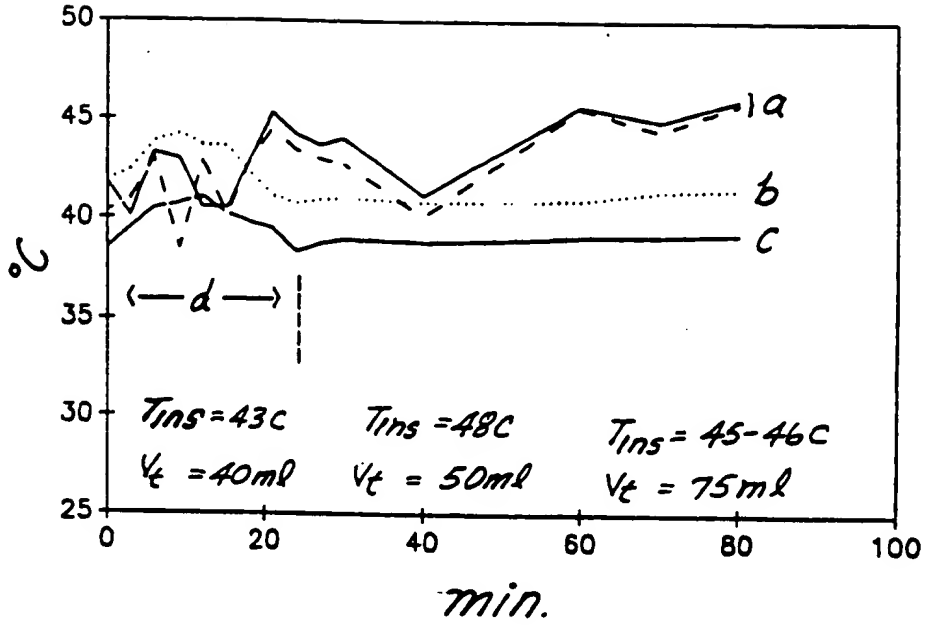

50
45
40
35
30
25
°C
0
20
40
60
80
100
min.
a
b
c
d
Tins=43C
Vt =40ml
Tins =48C
Vt = 50ml
Tins= 45-46C
Vt = 75ml

Fig. 30.

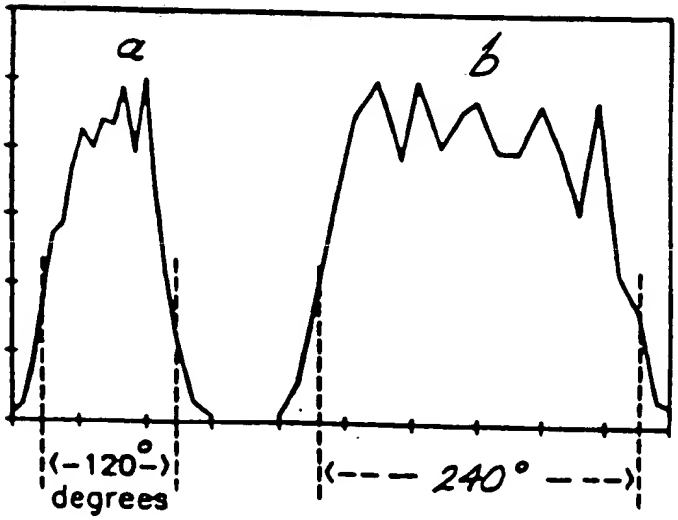

a
b
(-120°-)
degrees
(--- 240° ---)

Fig. 31.

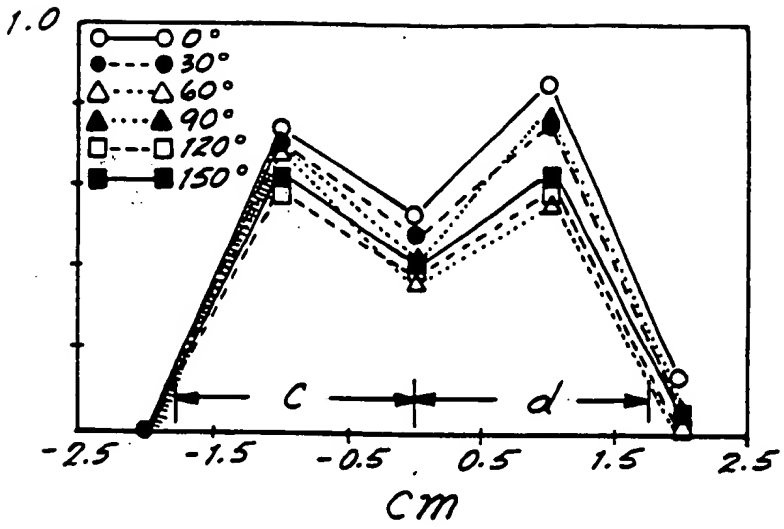

1.0
0°
30°
60°
90°
120°
150°
C
d
-2.5
-1.5
-0.5
0.5
1.5
2.5
cm

Fig. 32.

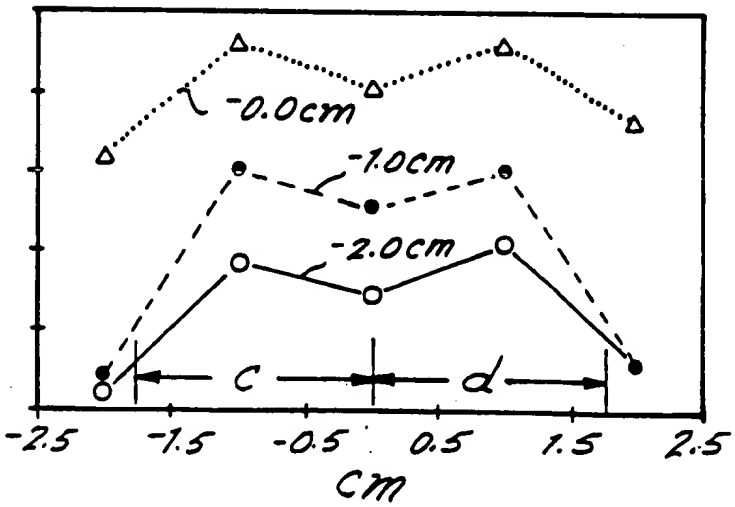

-0.0cm
-1.0cm
-2.0cm
C
d
-2.5
-1.5
-0.5
0.5
1.5
2.5
cm

Fig. 33.

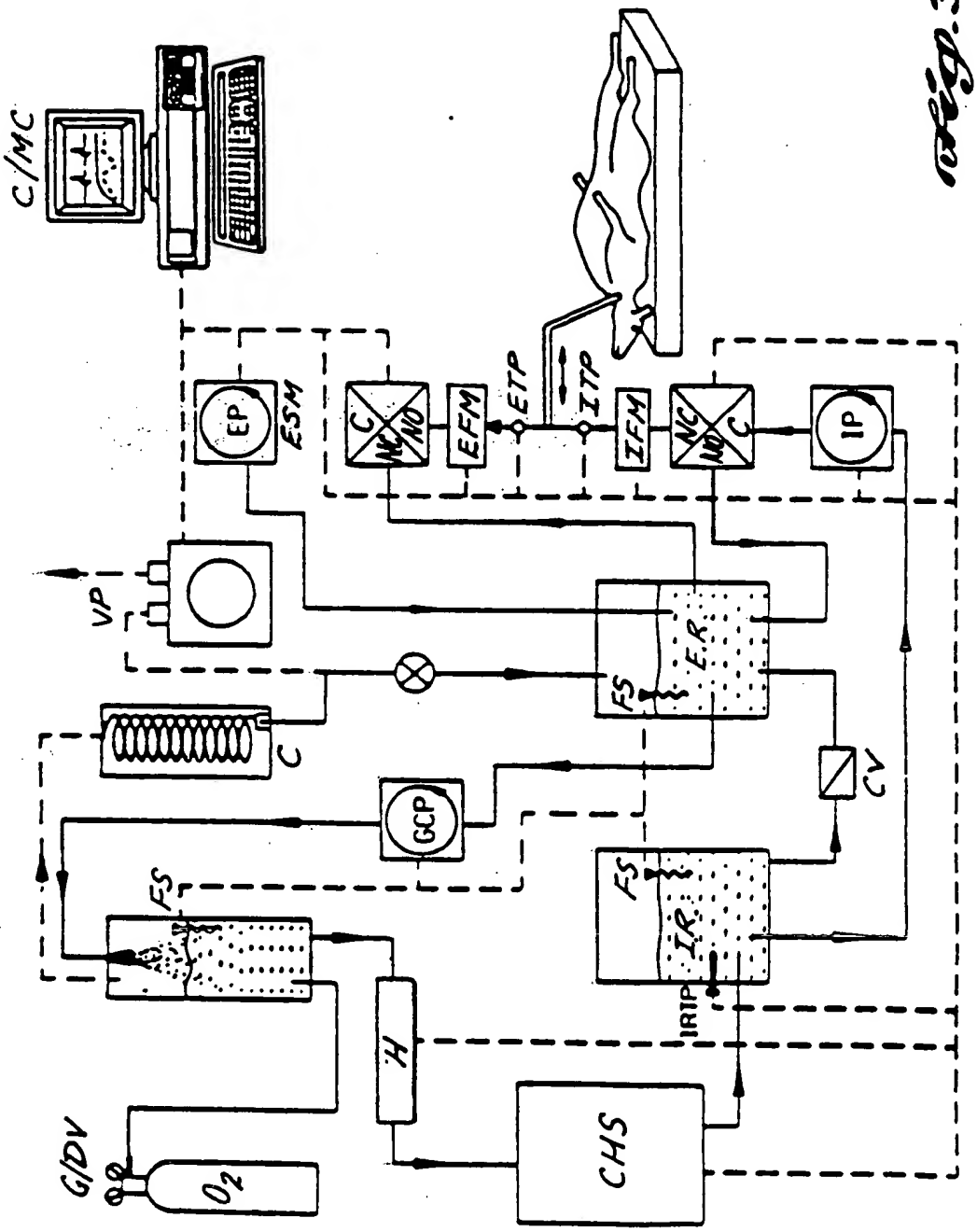

C/MC
EP
ESM
C
NC
NO
EFM
ETP
ITP
IFM
NC
NO
C
IP
VP
FS
E.R.
C
CV
GCP
FS
FS
I.R.
IRTP
H
G/DV
O2
CHS

Fig. 34.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04035

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (4): A61M 5/00
U.S. Cl. 604/113

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	604/28, 29, 31, 96, 101, 102, 113; 128/24A, 207.14, 207.15, 913

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 2,936,761 (SNYDER) 17 May 1960 Note dual cannulae in Figure 2).	58
Y	US, A, 3,358,677 (SHELDON) 19 December 1967 Note at column 2, lines 27-29 for saline use.	11, 31
Y	US, A, 4,046,139 (HORN) 06 September 1977 Note temperature probe in Figure 4.	51, 52
X Y	US, A, 4,233,984 (WALLING) 18 November 1980 Note catheter in Figure 1.	48, 49, 53, 56 50, 51, 54
A	US, A, 4,315,514 (DREWES ET AL) 16 February 1982, note columns 1-3.	1-47
A	US, A, 4,323,056 (BORRELLI ET AL) 06 April 1982, note column 1-column 3, line 64).	1-47
A	US, A, 4,657,532 (OSTERHOLM) 14 April 1987 Note column 1-column 4, line 48.	1-47

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 November 1989	18DEC 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Adam J. Cermak

Form PCT/ISA/210 (second sheet) (Rev 11-87)

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GR	Greece
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
PL	Poland
RO	Romania
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America